THE

AMERICAN JOURNAL

OF THE MEDICAL SCIENCES

APRIL, 1939

ORIGINAL ARTICLES.

THE INFLUENCE OF ACID AND ALKALINE SALTS UPON THE BLOOD IN HYPOCHROMIC ANEMIA TREATED BY IRON PARENTERALLY.

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Many investigators agree that achlorhydria interferes with the absorption of iron in certain cases of iron-deficiency anemia. Mettier and Minot[3] demonstrated that in cases of chronic hypochromic anemia iron administered orally produced more rapid hemoglobin regeneration when the gastroduodenal contents had a low rather than a relative high pH. Recent studies by Kellogg and Mettier[2] indicate that in some anemias due to chronic blood loss from peptic ulcer the alkalinization process associated with a Sippy regimen inhibits the absorption of iron contained in food. The following observations were made in order to determine if the oral administration of acid or alkaline salts in sufficient quantity to alter significantly the pH of the urine, affected the *utilization* of parenterally administered iron. Under the conditions of the experiments the influence of the acidity of the gastro-intestinal tract upon the absorption of iron was eliminated.

Method. Eleven cases of hypochromic anemia, or iron deficiency, were studied. Table 1 gives a brief clinical résumé of these cases.

The patients received a basal diet low in iron. The reticulocytes were counted daily. Venous blood was obtained every other day and prevented from clotting with oxalate. The number of red blood cells, hemoglobin percentage and, according to the method of Wintrobe, the hematocrit, mean corpuscular volume and mean corpuscular hemoglobin concentration were determined on this blood. The hemoglobin was determined with the Sahli apparatus calibrated so that 100% hemoglobin was equivalent to 15.6 gm. per 100 cc. of blood, or 20.9 vol. % oxygen capacity (Van Slyke).

The observations on each of the cases followed a preliminary control period of about 1 week, during which time it was observed that the hemoglobin and hematocrit values remained stationary and that the percentage of reticulocytes was not significantly elevated. In all cases obvious blood loss had ceased for at least one

TABLE 1.—SUMMARY OF 11 CASES OF HYPOCHROMIC (IRON DEFICIENCY) ANEMIA.

Case No.	Age.	Sex.	Initial R.B.C. (in mil.).	Initial hemoglobin, %.	Etiologic factors and remarks.
1	76	F	3.06	32.5	Uterine bleeding; poor diet; edentulous; gastric anacidity after injection of histamine.
2	19	M	1.975	33.5	Chronic blood loss from duodenal ulcer; gastric hyperacidity.
3	59	F	3.24	39.0	Chronic blood loss from carcinoma of colon; gastric anacidity after injection of histamine.
4	47	F	2.92	24.0	"Idiopathic" hypochromic anemia; menorrhagia; dysphagia; poor diet; gastric anacidity after injection of histamine.
5	58	M	3.06	48.0	Chronic blood loss from duodenal ulcer; chronic alcoholism; asymptomatic tertiary syphilis; normal gastric acidity.
6	31	M	2.06	33.0	Chronic blood loss from duodenal ulcer; normal gastric acidity.
7	63	M	3.34	31.0	Chronic blood loss from carcinoma of stomach; gastric anacidity after injection of histamine.
8	36	M	3.13	58.0	Chronic blood loss from duodenal ulcer; normal gastric acidity.
9	45	F	2.79	26.0	"Idiopathic" hypochromic anemia; menorrhagia; hemorrhoids; gastric anacidity after injection of histamine.
10	79	F	4.045	44.5	Malnutrition; low gastric acidity after injection of histamine.
11	48	M	4.05	29.5	Chronic blood loss from duodenal ulcer; gastric hyperacidity.

week before control observations were begun and there was no evidence of blood loss during the periods of observation. Guaiac tests were performed on the stools daily. After the control period iron was administered intramuscularly in the form of green iron and ammonium citrates (U. S. P.), 0.1 gm. daily or twice daily for a 20- to 32-day period. Some patients occasionally experienced toxic reactions with the larger dose. During the first half of this period the patient was given 24 gm. of sodium bicarbonate by mouth daily. This was given in 6 equal doses at 3-hour intervals during the day. During the second half of the period of iron therapy the patient was given 4 gm. of ammonium chloride by mouth daily, divided in 4 equal doses at 4-hour intervals. On 2 occasions this procedure was reversed.

With the basal diet which the patients received, the pH of the urine could be readily changed with acid or alkaline salt in the amounts mentioned above. During the period of alkali therapy the urine pH was maintained at 8 or above and during the period of acid therapy at 6 or below.

Results. Each of the 11 patients showed a gain in weight during the 10- to 16-day period of alkalinization and in some instances obvious edema developed. The average weight gained during this period was 7.4 pounds per individual. The greatest weight gain of

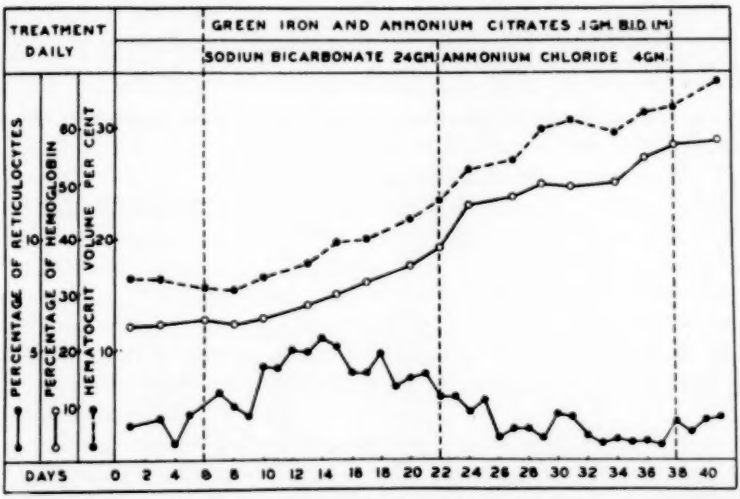
TREATMENT DAILY
GREEN IRON AND AMMONIUM CITRATES 1 GM. B.I.D. (M)
SODIUM BICARBONATE 24GM. AMMONIUM CHLORIDE 4GM.
PERCENTAGE OF RETICULOCYTES
PERCENTAGE OF HEMOGLOBIN
HEMATOCRIT VOLUME PER CENT
DAYS 0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40

FIG. 1.—Case 4 (Tables 1 and 2). This figure shows the influence of the oral administration of alkaline and acid salts upon blood formation, in a case of hypochromic anemia receiving iron parenterally. There was an initial reticulocyte response to the administration of iron and an increase in the hemoglobin and hematocrit values. Note the "apparent" more rapid hemoglobin formation du ing the period in which the acid salt was given but the absence of any second reticulocyte response.

any one person was 15 pounds. Conversely, all individuals showed a reduction in weight while receiving the acid salt. This was especially marked when the 10- to 16-day period of acid medication immediately followed the period of alkali therapy. The average weight lost during the acidifying period was 6.1 pounds per individual. These observations are in accordance with the results of other workers on the effects of a high sodium or high ammonium chloride intake, particularly in the presence of protein deficit.

Figure 1 shows the pertinent hematologic data in a typical case. In all instances the rise of hemoglobin was more marked during the time the acid salt was fed. When the data for all the cases were tabulated to represent a single average case the increase in

hemoglobin was 5.3% during the alkalinization period and 9.2% during the acidification period of the same duration. For various reasons, however, it cannot be concluded from this that the utilization of injected iron was greater when an acid salt was administered than when an alkaline salt was given.

It was observed in all instances that there was a rapid increase in hemoglobin and hematocrit values upon shifting from alkaline to acid salts. It was also noted that with a shift from neutral to alkaline and from acid to alkaline there was always a small immediate decrease in the hemoglobin and hematocrit values. It, therefore, appears that the regeneration of hemoglobin was *not* more rapid when the acid salt was given but that the greater increase of hemoglobin was due to a shift in plasma volume. A reticulocyte response

TABLE 2.—UTILIZATION OF INTRAMUSCULARLY ADMINISTERED IRON IN 11 CASES OF HYPOCHROMIC ANEMIA.

Case No.	Estimate of total grams circulating iron before treatment.	Estimate of total grams circulating iron after treatment.	Total grams iron administered.	Per cent utilization of iron.
1	0.890	1.539	0.730	89
2	1.323	1.971	0.730	77
3	0.951	1.278	0.608	54
4	0.537	1.213	0.973	69
5	1.194	1.548	0.426	83
6	1.469	1.766	0.441	67
7	0.683	0.918	0.385	61
8	1.436	1.853	0.502	83
9	0.564	1.070	0.699	81
10	0.827	1.208	0.608	63
11	0.832	1.209	0.730	52
Average	...	...	...	70

was observed in all cases when iron was first administered, but a second reticulocyte response never occurred when the acid salt was substituted for the alkaline one. The abrupt rise in the hemoglobin value observed during the period of acid salt administration is quite different from the usual gradual response of hemoglobin to iron administered by the parenteral route. Evidence from 2 cases not included in this report suggests that this phenomenon occurs regardless of whether iron is given or not.

The percentage utilization of iron given intramuscularly in these cases compares favorably with that shown by Heath, Castle and Strauss,[1] and Whipple and Robscheit-Robbins.[4] The observations were not carried out quite long enough after the cessation of iron therapy to obtain the complete rise of hemoglobin which the injected iron might have been capable of producing. An approximation of the total grams of circulating iron in the blood before and after treatment was calculated from the hemoglobin values and the blood volume. It was assumed that hemoglobin contains 0.35% iron.

The blood volume was calculated by multiplying the square meters of body surface, obtained from the height and weight, by 2423.[1] In the 11 cases studied, the utilization of the injected iron ranged from 52 to 89%, with an average of 70% (Table 2). Two additional cases of hypochromic anemia which were unsuitable for the acid and alkaline salt studies, because of chronic gastro-intestinal hemorrhage, showed only 29 and 32% "utilization" of injected iron.

Comment. The present observations demonstrate that the administration of either an acid or alkaline salt does not affect the utilization of injected iron in patients with hypochromic anemia. Sudden shifts in the hematocrit values occurred coincident with changes in the pH of the urine and body weight. The evidence at hand suggests that these sudden changes were due to changes in plasma volume and not to improved or impaired utilization of the injected iron. Since the iron was administered intramuscularly, the possibility of the acidity of the gastroduodenal contents affecting the absorption of the iron was eliminated. To avoid errors in drawing conclusions regarding hemoglobin regeneration from iron therapy, in cases with iron deficiency, it must be recognized that the acidity of the diet when affected by the administration of acid or alkaline salts has a significant influence on the plasma volume. This is especially true when the blood formation is being studied over relatively short periods and the importance of small changes is being stressed.

Although it is rarely necessary to give iron parenterally in an iron-deficient individual, the present observations reëmphasize the fact that injected iron apparently is used almost quantitatively for hemoglobin regeneration. When the percentage utilization falls below 50% it strongly suggests concomitant blood loss.

Conclusions. 1. The oral administration of acid or alkaline salts in sufficient quantity to cause significant body weight and urinary pH changes does not affect the utilization of iron injected intramuscularly in cases of hypochromic anemia.

2. The changes in plasma volume accompanying a sodium bicarbonate or ammonium chloride regimen must be considered when conclusions are drawn about hemoglobin regeneration in hypochromic anemia.

3. In 11 cases of hypochromic (iron deficiency) anemia an average of 70% of the intramuscularly administered iron was utilized for hemoglobin regeneration.

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PRESERVED CITRATED BLOOD "BANKS" IN RELATION TO TRANSFUSION IN THE TREATMENT OF DISEASE WITH SPECIAL REFERENCE TO THE IMMUNOLOGIC ASPECTS.

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Transfusion of preserved citrated blood from "banks" has become increasingly popular within recent years. The usual method employed in the United States is that of the Cook County Hospital,[3] consisting in the addition of 14 cc. of a sterile 2.5% solution of chemically pure sodium citrate in physiologic saline solution to each 100 cc. of blood, and preservation at 4° to 6° C. in a refrigerator. This gives a 0.35% concentration of sodium citrate for the prevention of coagulation and after typing, sterility and Wassermann tests, the blood is ordinarily available for transfusion over a period of 10 days to several weeks.

Physiologically and according to clinical experience, such preserved citrated blood is apparently satisfactory for the restoration of blood volume and superior to saline, glucose and acacia solutions in the treatment of severe traumatic hemorrhage and shock. Whether or not the erythrocytes are sufficiently preserved to carry on internal respiration is debatable; likewise the question as to whether or not the platelets and coagulating principles are sufficiently preserved for the treatment of the thrombocytopenic purpuras and other hemorrhagic dyscrasias.

While these matters will be considered later, my special purpose is to discuss preserved citrated blood in the treatment of acute and chronic infections with special reference to the septicemias, and I may mention at the outset that available data indicate that it should not be used for these purposes when more than 2 to 3 days old.

The Immunologic Aspects of Transfusion. It is sometimes stated that the chief value of blood transfusion in the treatment of septic states with or without associated septicemia is to combat the secondary anemia and that it is not indicated or required until or unless the hemoglobin is reduced to about 40% with a corresponding reduction in erythrocytes.

With this I do not agree. Septicemia at least is apparently the result of a breakdown or exhaustion of the normal clearing mechanism of the blood, not infrequently the result of continuous accession of bacteria and their toxic products from foci of infection of the fixed tissues. I have gradually gained the conviction that one of the most important reasons for frequent transfusions in the treat-

ment of septic states, and especially those with an associated septicemia, is to furnish specific and non-specific immune substances in the blood of the donor, which may have become reduced or exhausted in the hard-pushed patient or recipient. Furthermore, it is not unlikely that the leukocytes of *fresh* blood may serve a useful therapeutic purpose. Therefore, without questioning the value of transfusion in septic states from the standpoint of combating secondary anemia, it seems to me that proper emphasis must be placed upon its possible additional value from the immunologic standpoint and if this is true, the therapeutic status of preserved citrated blood should be examined from both angles.

Briefly and in general terms it may be stated that normal or natural resistance and immunity to infection is due in part to specific antitoxins and such sensitizing antibodies as agglutinins, opsonins and bacteriolysins that may be present in the blood. To these, from the non-specific standpoint, must be added complement, leukins (from leukocytes) and plakins (from platelets). Among these the opsonins are of particular importance because of the rôle they play in phagocytosis, not only by the microphages of the blood and fixed tissues, but by the cells of the reticulo-endothelial system as well. Furthermore, agglutinins likewise facilitate both phagocytosis and bacteriolysis *in vivo* and complement is especially important in both particulars, while the leukins and plakins are apparently largely responsible for the normal non-specific bactericidal activity of the blood. Indeed it would appear that the chief therapeutic value of non-specific immuno-transfusions conducted by the intravenous injection of the donor with 100 million killed typhoid bacilli in vaccine a few hours before transfusion is due in part not only to the transfer of more than normal numbers of leukocytes from donor to patient but likewise to additional amounts of these normal or natural non-specific bactericidal substances.

Certainly we have ample data for indicating that these specific and non-specific mechanisms are responsible for the remarkable capacity of the blood for normally clearing itself of organisms and especially because of phagocytosis by the cells of the recticulo-endothelial system. In septic states, especially septicemia, it is a logical deduction that this clearing mechanism is reduced or exhausted. If this is true, one of the purposes of transfusion in treatment should be to supply the hard pressed patient with as many of these specific and non-specific factors as possible. One cannot now state that natural antitoxins for the several exotoxins of staphylococci and streptococci are reduced or exhausted in acute infections and especially septicemia, but this may be logically inferred. While it is admittedly difficult to measure complement in relation to bacteriolysis, yet this is comparatively easy in relation to hemolysis and I am convinced on this basis that it is frequently reduced below average normal levels in staphylococcus and streptococcus septi-

cemias. Indeed, I believe that one of the purposes of transfusion is to supply the patient with the complement of the donor; and I believe the same applies to opsonins, which likewise have been found to undergo reduction below average normal and especially in acute fulminating infections.

Additional observations on the total bactericidal activity of whole blood for staphylococci, streptococci, pneumococci and B. typhosus have indicated that in a large percentage of cases there is a demonstrable reduction. This, however, I have never been able to measure with acceptable accuracy; but it is probably due not only to reduction in complement and opsonins, but probably to bacteriolysins and the non-specific leukins and plakins as well.

If one of the purposes of transfusion in the treatment of septic states is to supply the patient with these specific and non-specific immunologic principles, in addition to combating secondary anemia, the question at issue is whether or not transfusion supplies them in amounts of therapeutic value, in view of the fact that normal blood admittedly carries but small amounts of these substances. Indeed, the difference of opinion that exists on the clinical value of transfusion in the treatment of acute and chronic infections is largely on this basis. Insofar as specific antibodies are concerned, it would appear that the blood of convalescent or actively immunized donors is to be preferred on the basis of supplying larger amounts, and for this reason specific immuno-transfusions are always to be preferred when possible.

Furthermore and especially in relation to preserved citrated blood in "banks" for the treatment of acute and chronic infections, and especially septicemias, the important question is whether or not immune bodies, as well as functionally active erythrocytes and platelets are sufficiently preserved to be of value. My own studies have been mostly confined to complement, opsonins, total bactericidal activity and the phagocytic activity of neutrophils; insofar as these are concerned the results have indicated that preserved blood is apparently of no value after 2 to 3 days' preservation, as previously stated.

Effects of Sodium Citrate on Complement. As is well known, human complement deteriorates rapidly, even when kept at 4° C. unless special methods for preservation are employed. For example, as shown in Table 1, the complement of the sera of 3 specimens of human blood left on the clots and kept at 4° C. in a refrigerator showed marked deterioration at the end of 5 days.

Deterioration, however, is observed to a much lesser degree in citrated human blood kept at 4° to 6° C. Opponents to the citrated or indirect method of blood transfusion have advanced the objection that sodium citrate in 0.25 to 0.35% concentration is destructive for human complement. This, however, does not appear to be true; indeed, the reverse appears to be the case as sodium citrate

in 0.35% concentration apparently preserves the complement of human blood in a remarkable degree, analogous to the preservation of guinea pig complement for the Wassermann test by sodium

TABLE 1.—THE HEMOLYTIC ACTIVITY OF SERUM LEFT ON CLOTS AND KEPT AT 4° C.

Intervals.	A.	B.	C.
Immediately	0.1*	0.1	0.05
24 hours	0.1	0.1	0.1
48 "	0.1	0.1	0.1
72 "	0.1	0.2	0.1
5 days	0.4	0.5	0.4
7 "	†		

* Approximately smallest amount of serum giving complete hemolysis of 0.5 cc. of 2% suspension of sheep corpuscles sensitized with 2 units of hemolysin.
† No hemolysis with 0.5 cc. of serum (the largest amount employed).

acetate and sodium chloride. For example, as shown in Table 2, the hemolytic activity of the complement for sensitized sheep corpuscles in the citrated (0.35%) bloods (kept at 4° to 6° C.) of 6

TABLE 2.—THE HEMOLYTIC ACTIVITY OF PLASMA OF PRESERVED CITRATED BLOODS FOR SENSITIZED SHEEP CORPUSCLES.

Intervals.	A.	B.	C.	D.	E.	F.
Immediately	0.1*	0.1	0.1	0.05	0.05	0.05
24 hours	0.1	0.2	0.1	0.05	0.05	0.05
48 "	0.1	0.2	0.2	0.05	0.05	0.05
72 "	0.1	0.2	0.2	0.05	0.05	0.05
5 days	0.1	0.2	0.2	0.05	0.05	0.05
7 "	0.2	0.2	0.2	0.05	0.05	0.05
14 "	0.3	0.3	0.3	0.15	0.05	0.05
21 "	0.3	0.3	0.3	0.25	0.1	0.1

* Approximately smallest amount of plasma of citrated bloods preserved at 4 to 6° C. giving complete hemolysis of 0.5 cc. of 1 to 2% suspension of sheep corpuscles sensitized with 2 units of antisheep hemolysin.

donors showed some reduction 24 to 48 hours after collection in 2 of them (B and C), but in general terms the activity of the complement of all 6 was well preserved up to 2 to 3 weeks (longer periods not being employed) when some deterioration was observed.

TABLE 3.—THE PRESERVATION OF GUINEA PIG COMPLEMENT WITH 0.35% SODIUM CITRATE AT 2° TO 4° C.

Intervals.	Citrated complement.	Control complement.
Immediately	0.05*	0.05
24 hours	0.05*	0.05
48 "	0.05*	0.05
72 "	0.05*	0.05
5 days	0.05*	0.1
7 "	0.05*	0.2
14 "	0.1	0.4

* Approximately smallest amount of complement giving complete hemolysis of 1 cc. of 2% suspension of sheep corpuscles sensitized with 2 units of antisheep hemolysin.

The same has been found true of guinea pig complement, as shown in Table 3. In this experiment a portion of the pooled complement sera of 3 guinea pigs was kept at 2° to 4° C. and showed

some deterioration in hemolytic activity for sensitized sheep corpuscles at the end of 5 days, whereas a citrated portion (0.35°) kept under identical conditions and titrated for hemolytic activity at the same intervals and under identical conditions showed no deterioration until about 14 days.

At first, I thought that these results might be due to hemolytic activity on the part of sodium citrate itself; but, as shown in Table 4, even 1 cc. of a 50% solution in normal saline equivalent to 0.5 gm. was without hemolytic effects for 0.5 cc. of a 1% suspension of washed sheep cells in a total volume of 3 cc. at 37° C. in a water bath for 1 hour. Furthermore, when portions of the citrated plasmas of the 6 donors (listed in Table 2) were heated in a water bath at 55° C. for 30 minutes at the end of 14 days' preservation at 4° to 6° C., it was found that hemolytic activity for sensitized sheep corpuscles was completely lost, even in doses as high as 0.5 cc. of undiluted plasma, indicating that heating had inactivated the plasmas presumably because of destruction of complement.

However, 0.2 to 0.3 cc. of a 5% solution of sodium citrate were destructive or anticomplementary for 0.4 cc. of 1 to 30 guinea pig complement (Table 4). It is apparent, therefore, that sodium citrate is destructive for guinea pig complement in high dilutions, but that 0.35% is much less destructive for undiluted guinea pig and human complements.

TABLE 4.—THE HEMOLYTIC AND ANTICOMPLEMENTARY EFFECTS OF SODIUM CITRATE.

Hemolytic activity.		Anticomplementary activity.*	
50% sol., cc.	Hemolysis.	5% sol., cc.	Hemolysis.
0.1	—†	0.05	No effect; C.H.‡
0.2	—	0.1	No effect; C.H.‡
0.3	—	0.2	Slight effect; M.H.
0.4	—	0.3	Marked effect; N.H.
0.5	—	0.4	Marked effect; N.H.
0.6	—	0.5	Marked effect; N.H.
0.7	—	0.6	Marked effect; N.H.
0.8	—	0.7	Marked effect; N.H.
0.9	—	0.8	Marked effect; N.H.
1.0	—	0.9	Marked effect; N.H.

* Effects on the hemolytic activity of 0.4 cc. of 1 to 30 guinea pig complement for 0.5 cc. of a 1% suspension of sensitized sheep corpuscles in a total volume of 3 cc. at 37° C. for 1 hour.

† No hemolytic effects on 0.5 cc. of 1% suspension of washed sheep corpuscles in a total volume of 3 cc. at 37° C. for 1 hour.

‡ C.H. = complete hemolysis; M.H. = marked hemolysis; N.H. = no hemolysis.

Effect of Sodium Citrate on the Bactericidal Activity of Preserved Blood. The normal or natural bactericidal activity of whole blood *in vitro* may be ascribed to: (*a*) the presence of specific bacteriolysins requiring the presence of complement for their activity; (*b*) non-specific bactericidans (probably leukins and plakins) which are effective without the presence of complement; and (*c*) phagocytosis by the neutrophils aided by opsonins which are quite similar to complement in their physical properties.

Three-cc. amounts of the citrated blood (0.35%) of 3 donors were placed in 3 sterile test tubes immediately after collection and seeded with 1 drop of 18- to 24-hour broth culture of S. aureus, a beta hemolytic streptococcus of Group A and B. coli respectively. The blood cultures were incubated at 37° C. for 48 hours, after which they were examined by stained smears and the amount of growth estimated by the number of organisms found. The 3 citrated bloods were kept at 4° to 6° C. and the tests repeated at the intervals up to 21 days (Table 5).

TABLE 5.—THE BACTERICIDAL ACTIVITY OF WHOLE PRESERVED CITRATED BLOOD.

	Donor A.			Donor B.			Donor C.		
Intervals.	Staph.	Strept.	B. coli.	Staph.	Strept.	B. coli.	Staph.	Strept.	B. coli.
Immediately	+*	+	+	+	+	+	+	+	+
24 hours . .	+	+	+	+	+	+	+	+	+
48 " . .	+	+	+	+	+	+	+	+	+
72 " . .	+	+	+	+	+	+	+	+	+
5 days . .	+	+	+	+	+	+	+	+	+
7 " . .	++	+	++	+	+	+	+	+	+
14 " . .	++	+	+	+	++	+	++	++	+
21 " . .	++	++	++	++	++	++	++	++	++

* + = scanty growth; ++ = moderately heavy growth.

It will be noted that even the fresh citrated bloods of each donor seeded with the 3 organisms immediately after collection were not completely bactericidal as scanty growths occurred in all. But at the end of 7 to 21 days (longer intervals not being employed) all 3 citrated bloods kept at 4° to 6° C. showed some loss in total bactericidal activity for one or more of the organisms employed. This reduction in bactericidal activity may have been due to gradual inactivation of complement and opsonins, some loss of bacteriolysins and the non-specific leukins or plakins or all of these, as the tests were of such a character as only roughly to measure the total antibacterial activity of the 3 citrated bloods; but at all events the results indicate that citrated blood kept at 4° to 6° C. tends to lose in total antibacterial properties in from 7 to 21 days.

Effect of Sodium Citrate on the Phagocytic Activity of Preserved Blood. Opsono-phagocytic tests were conducted with 3 citrated (0.35%) bloods employing S. aureus, a beta hemolytic streptococcus (Group A) and B. coli according to the method of Boerner and Mudd[1] immediately after collection and at the intervals up to 21 days (kept at 4° to 6° C.), shown in Table 6.

A slight reduction in phagocytic activity was noted in some instances 24 hours after collection and citration of the 3 bloods, but more marked reduction was noted in some instances as early as 72 hours after collection. This became more marked on or about the fifth day, followed by almost total absence of phagocytosis on and after the seventh day of preservation.

Similar results were observed in the opsonic indices for all 3 organisms with the blood of Donor A (Table 7).

These marked changes in the opsono-phagocytic activities of the 3 citrated bloods preserved at 4° to 6° C. may have been due in part to deterioration of opsonins, but undoubtedly were mainly and most likely entirely due to autolytic changes in the neutrophils. Indeed, these changes were already well pronounced on the fifth day and so marked by the seventh as to make the phagocytic determinations very inaccurate or entirely impossible.

TABLE 6.—THE PHAGOCYTIC INDICES OF PRESERVED CITRATED HUMAN BLOOD.*

Intervals.	Donor A.†			Donor B.			Donor C.		
	Staph.	Strept.	B. coli.	Staph.	Strept.	B. coli.	Staph.	Strept.	B. coli.
Immediately	38	11	16	10	13	20	28	17	22
24 hours	32	10	14	10	19	22	24	14	18
48 "	31	12	15	12	12	21	21	16	20
72 "	32	9	12	10	8	5	15	11	14
5 days	26	4	9	6	2	1	12	5	8
7 "	—‡	—	—	—	—	—	6	—	3
14 "	—	—	—	—	—	—	—	—	—
21 "	—	—	—	—	—	—	—	—	—

* Percentage of phagocytic polymorphonuclear neutrophils (100 cells examined).
† S. aureus; beta hemolytic streptococcus (Group A); B. coli.
‡ Examinations could not be made because of autolytic changes in neutrophils.

TABLE 7.—THE OPSONIC INDICES OF PRESERVED CITRATED BLOOD OF DONOR A.

Intervals.	Staph. aur.	Beta hemolytic strept.	B. coli.
Immediately	1.5*	0.3	1.0
24 hours	1.5	2.0	2.2
48 "	2.5	1.5	2.1
72 "	1.5	1.0	0.5
6 days	0.2	—	0.1
14 "	—	—	—
21 "	—	—	—

* Average number of organisms per phagocyte; — = examination could not be made because of autolytic changes in the neutrophils.

Effects of Sodium Citrate on the Cellular Elements of Preserved Blood. This led to a more detailed study of changes in the cellular elements (erythrocytes, leukocytes and platelets) of preserved citrated (0.35%) bloods of donors kept at 4° to 6° C. with special reference to the leukocytes.

Immediately after collection and citration of the blood of Donors D, E and F, listed in Table 2, smears were made and stained; smears were also prepared at the intervals up to 14 days shown in this table.

These were examined by Dr. Frank W. Konzelmann, who reported as follows: "Forty-eight hours after collection the *erythrocytes* already showed some evidence of disintegration indicated by swelling and the presence of shadowy forms poor in hemoglobin. At later intervals these changes were more pronounced along with the presence of shrunken or pyknotic cells so that by the end of 14 days almost 30% were shadows with loss of some hemoglobin, swollen and apparently very fragile. The *leukocytes* began to show evi-

dences of disintegration with reduction in numbers as early as 24 hours after collection and after 48 hours the chromatin showed less distinct nuclear markings while the cytoplasm became basophilic. Finally at the end of 14 days the cytoplasm had become completely destroyed with only swollen masses of chromatin remaining. The *platelets* showed distinct clumping immediately and 24 hours after collection with evidence of deterioration in the latter. At the end of 48 hours they became scarce and after 5 days only blue chromatin masses remained."*

A macroscopic examination of the plasma of Donors C, D, E and F secured by centrifuging 3 cc. amounts of blood immediately after collection and at the intervals up to 21 days (Table 8) showed no

TABLE 8.—SPONTANEOUS HEMOLYSIS OF CITRATED BLOOD KEPT AT 4° TO 6° C.

Intervals.	Hemolysis.			
	Donor C.	Donor D.	Donor E.	Donor F.
Immediately	None	None	None	None
24 hours	None	None	None	None
48 "	None	None	None	None
72 "	None	None	None	None
5 days	Very slight	None	Very slight	None
7 "	Slight	Slight	Slight	Slight
14 "	Marked	Marked	Marked	Marked
21 "	Marked	Marked	Marked	Marked

demonstrable amounts of free hemoglobin until about the fifth day of preservation which became more definite by the seventh day and quite marked by the end of 2 and 3 weeks. None was frozen so that hemolysis could not be ascribed to alternate freezing and thawing. It is highly probable that hemolysis began at earlier intervals than those recorded, because the readings were based entirely on naked eye appearance of the plasma and ordinarily is not detectable until the blood is centrifuged.

Differential leukocyte counts were made of the citrated bloods of Donors D, E and F immediately after collection and at the intervals up to 14 days shown in Table 9. On account of the disintegrative morphologic changes, beginning as early as 24 to 48 hours after collection and citration, no attempt was made to differentiate lymphocytes from monocytes but these are listed in the table under the designation of "mononuclear cells." It will be noted that in all 3 of the specimens the neutrophils showed reduction in numbers as early as 24 hours after collection and citration. The percentages of

* While this paper was in course of publication, J. E. Rhoads and L. M. Panzer (The Prothrombin Time of "Bank Blood," J. Am. Med. Assn., **112**, 309, 1939) found on the basis of the Quick method, that blood that has been in a bank a week or more would be practically useless in the treatment of the acute prothrombin deficiency encountered in jaundiced patients not adequately treated with vitamin K and bile salts. In their opinion, blood in a bank for 3 days would probably be of some slight value but would be so inferior to freshly drawn blood that they recommend that only the latter be used when transfusion is intended to combat the hemorrhagic tendency in jaundice.

"mononuclear cells" are only approximate; fluctuations and apparent increase in numbers has been probably due to the fact that nuclei of neutrophils with degenerated and lost cytoplasm have been included under this designation.

TABLE 9.—DIFFERENTIAL LEUKOCYTE COUNTS OF PRESERVED CITRATED BLOOD.

	Neutrophils.			Mononuclear cells.			Eosinophils.			Basophils.		
Intervals.	D.	E.	F.	D.	E.	F.	D.	E.	F.	D.	E.	F.
Immediately	29*	56	59	70	43	41	0	1	0	1	0	0
24 hours . .	9	42	43	91	55	55	0	1	1	0	2	1
48 " . .	9	24	28	91	76	72	0	0	0	0	0	0
72 " . .	12	36	—	88	64	—	0	0	—	0	0	—
7 days . .	7	40	—	93	60	—	0	0	—	0	0	—
14 " . .	5	44	34	93	56	66	1	0	0	1	0	0

* Percentages: 50 to 100 cells counted.

Discussion. Without attempting any review of the literature on the properties of whole blood by direct transfusion *versus* citrated blood in the treatment of hemorrhage, the hemorrhagic diseases, acute and chronic infections and so on, it may be stated that the results of this study have not revealed any important changes in the cellular or immunologic contents of citrated blood used immediately or within a few hours of collection for transfusion purposes. To the best of my knowledge and experience *fresh* citrated human blood is just as applicable as whole blood by direct transfusion, although I believe the former yields a somewhat higher incidence of febrile and minor reactions.

But the results of the study seriously question the advisability of using citrated blood preserved for 2 to 3 days or longer. Unger[6] has stated that sodium citrate inactivates complement, renders erythrocytes more fragile, reduces opsonin and destroys the phagocytic activity of the neutrophils. Drinker and Brittingham[2] state that it renders erythrocytes more fragile and produces suggestive changes in the platelets. Mellon, Hastings and Casey,[5] and Lewisohn,[4] however, found that sodium citrate did not increase the fragility of erythrocytes or reduce the phagocytic activity of the leukocytes.

As previously stated, I do not believe that sodium citrate in concentration of 0.35% produces deleterious changes quickly enough to question the value of citrated blood given immediately or within a few hours of collection. But the changes apparent in erythrocytes in 48 hours and certainly after longer periods of preservation, should question the value of preserved citrated blood in the treatment of the anemias. Furthermore, since changes were apparent in the platelets both immediately and 24 hours after collection and citration, it is open to question whether preserved citrated blood should be used in the treatment of the thrombocytopenic and other purpuras where one purpose of transfusion is to supply the patient with coagulating principles.

Certainly preserved citrated blood shows sufficient disintegrative

and autolytic changes in the neutrophils to reduce sharply their phagocytic activities after 2 to 3 days' preservation at 4° to 6° C. and to question its value in the treatment of acute infections and especially septicemia, if it is believed, as I do, that the transfusion of healthy active leukocytes contributes an important factor to resistance.

As previously stated the complement of citrated human blood kept at 4° to 6° C. does not undergo any marked inactivation during the first 14 days of preservation but after this time it and the total bactericidal activity of the preserved blood for such organisms as S. aureus, beta hemolytic streptococcus and B. coli are reduced sufficiently to question the value of preserved blood in the treatment of the acute and chronic infections. Of course this is in regard to whatever value complement, specific (antibodies) and non-specific bactericidal substances (leukins and plakins) have in the treatment of infections with special reference to the septicemias. It is admitted that the amounts transfused in 200 to 500 cc. of blood are sufficiently small to question their value in treatment, but I personally believe that they are helpful and that blood transfusion in the treatment of infection is just as important from this immunologic aspect as it is in combating secondary anemia. At all events it would appear advisable always to select a convalescent or immunized donor whenever feasible, in order to transfuse as much specific antibodies as possible. It is not yet clear whether or not non-specific immunotransfusions are superior in curative activity to plain transfusions, but theoretically at least they should be, if it is granted that the patient derives additional benefit from the infusion of increased numbers of leukocytes as well as increased amounts of leukins, plakins and specific natural antibodies.

At all events, the results of the investigation have left me with the conviction that, while citrated human blood preserved up to 10 to 21 days at 4° to 6° C. may be useful in the treatment of acute hemorrhage and shock for the restoration of volume, it should not be used at all in the treatment of the anemias, hemorrhagic dyscrasias or infections, and certainly not after 2 to 3 days' preservation.

Summary. 1. While sodium citrate is slightly anticomplementary, the complement of citrated (0.35%) human blood, kept at 4° to 6° C., was well preserved for periods up to 14 to 21 days. The same has been found true of undiluted citrated guinea pig complement kept at 2° to 4° C.

2. The bactericidal activity of normal citrated human blood kept at 4° to 6° C. for S. aureus, beta hemolytic streptococcus and B. coli decreased after 7 to 21 days' preservation.

3. The phagocytic activity of the neutrophils of preserved citrated human blood kept at 4° to 6° C. for S. aureus, beta hemolytic streptococcus and B. coli was definitely reduced within 72 hours after collection of blood, becoming markedly so on or about the fifth day,

followed by almost total absence of phagocytic activity on and after the seventh day of preservation. This may have been due to deterioration of normal opsonins but was mostly due to autolytic and degenerative changes in the leukocytes.

4. The erythrocytes of preserved citrated human blood kept at 4° to 6° C. showed evidences of swelling and dehemoglobinization as early as 48 hours after collection with progressive degenerative changes up to 14 days when at least 30% were shadows, swollen and fragile.

5. The neutrophils of preserved citrated human blood kept at 4° to 6° C. showed evidences of disintegration with reduction in numbers as early as 24 hours after collection, with progressive disintegrative and autolytic changes up to 14 days (longer intervals of preservation not being employed).

6. The platelets of preserved citrated human blood kept at 4° to 6° C. showed distinct clumping immediately and 24 hours after collection with evidences of deterioration in the latter. At the end of 48 hours they became scarce and after 5 days only blue chromatin masses remained.

7. For reasons discussed it is believed that citrated human blood preserved at 4° to 6° C. may be useful in the treatment of acute hemorrhage and shock for the purpose of restoration of volume, but is inadvisable for the treatment of the anemias, the blood dyscrasias or infections, and certainly should not be employed for these purposes after 2 to 3 days' preservation.

* I am indebted to Miss Mary Werner, Miss Anna M. Rule, Mrs. Elsa R. Lynch and Miss Mary Howard for assistance in conducting this investigation.

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SULPHANILAMIDE THERAPY IN GONORRHEA.

REVIEW OF LITERATURE AND REPORT OF 298 CASES.

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Numerous reports have shown that sulphanilamide in large doses often effects a clinical cure of acute and chronic gonorrheal urethritis in the male. Various severe blood dyscrasias, cutaneous

and other reactions have occurred, and have served to warn that this drug is not to be used without careful supervision. Some authors have had results that were entirely unsatisfactory (Anwyl-Davies[1]); or have had no conspicuous success (Lees[15]), and others have had 60% of failures (Johnson and Pepper[13]); and others have claimed that sulphanilamide has revolutionized the treatment of gonorrhea. It is the purpose of the authors to present their results in a comparatively large series of cases (298), and to compare and correlate them with the other large series of cases that have been reported to date.

Dees and Colston,[7] the first to use sulphanilamide in gonorrhea, reported 47 cases, with 75% of cures. Reuter[23] reported clinical cure in 90% of 100 cases. Erskine, Johnson and Lloyd[8] reported early and marked improvement, with particularly excellent results when local treatment is used at the same time, in 100 cases. Crean,[6] using prontosil soluble and sulphanilamide, effected cures in 90 of 100 cases. Johnson and Pepper[13] had 60% of failures in 64 cases.

Table 1 shows the largest groups of cases as yet reported. In the series of 100 cases or more, of which there are 4, the proportion of cures has been high enough (76 to 90%) to be very impressive, even if one argues that these cases are only temporarily or symptomatically cured. The authors have found substantial confirmation of the

TABLE 1.—RESULTS OF SULPHANILAMIDE TREATMENTS OF GONORRHEA IN PUBLISHED CASE SERIES.

Author.	Number of cases.	Per cent of cures.
Dees and Colston[7]	47	75
Reuter[23]	100	90
Herrold[11]	30	50
Gruetz[10]	36	66
Anwyl-Davies[1]	19	Entirely unsatisfactory
Erskine, Johnson and Lloyd[8]	100	Early and marked improvement.
Crean[6]	100	90
Lees[15]	..	No conspicuous success, too toxic.
Johnson and Pepper[13]	64	40
Knight[14]	63	63
Orr[21]	134	87
Graham[9]	23 males	65
Graham[9]	13 females	18
Bush[4]	20	40
Ferguson, *et al.*	298	76

action of sulphanilamide in effecting a clinical, and probably a permanent bacteriologic cure, in 76% of 298 patients, and agree, with certain qualifications, that sulphanilamide has "revolutionized" the treatment of gonorrhea, at least in the male. The qualifications alluded to have their origin in our ignorance of the proportion of cases which will relapse or become carriers, and in our imperfect understanding of the mechanism of the drug's action and the reason for its failure in 30% or so of cases. Also, there is the possible additional drawback that a failure with sulphanilamide affects

adversely the ability of the patient to react favorably to other means of treatment. This is the belief of Crean.[6]

We have treated 298 sea-faring men, generally between the ages of 20 and 40, and in good physical condition, in the venereal disease wards of the U. S. Marine Hospital at Stapleton, Staten Island, New York. The first 100 patients were studied by the staff of the Venereal Disease Research Laboratory at the U.S.P.H.S. in Stapleton, and made the subject of a report by Van Slyke, Thayer and Mahoney.[24] In a group of 17 of these patients, Van Slyke *et al.* carried out special blood and urine studies in an effect to detect the approach of severe toxic manifestations attributable to the drug. These included red and white blood cell counts, hemoglobin content, red cell fragility determinations, spectroscopic examination for methemoglobin and sulphemoglobin, CO_2-combining power of the plasma, total non-protein nitrogen and NaCl content of the blood. Further, the studies included determination of the blood concentration of sulphanilamide as determined by the method of Marshall, Emerson and Cutting.[19] "As these procedures failed to presage toxic reactions or to display consistent blood changes (with the exception of the CO_2-combining power of the plasma), they were abandoned as a routine and used only as indicated in the remainder of the study" (Van Slyke *et al.*). The studies on the blood concentration of sulphanilamide, however, were influential in determining the increases in dosage decided upon by the research staff and ourselves.

1. *Relative Success in Acute as Compared With Chronic Cases.* Regarding the relative efficacy of sulphanilamide in chronic cases as compared with acute cases, Crean had excellent results (1 failure, a relapse) in 24 chronic cases, and Herrold cured 10 of 12 chronic cases. Reuter had about equal success with chronic as with acute cases. Knight, on the other hand, states that chronic gonorrhea lends itself less easily to relief by sulphanilamide. The Venereal Disease Research Laboratory at our hospital had only 1 failure among 36 chronic cases (97% successes), and had 77% of cures among the acute cases, but among the subsequent 198 patients studied on our wards, the proportion of failures among the chronic cases was slightly higher, and our combined figures for the 298 cases are 73% of successes in the acute cases (210 cases) and 83% successes in the chronic (88 cases), making the proportion of successes for the entire 298 patients 76%. (We regarded infections of less than 28 days' duration as acute cases, and the others as chronic.) It, therefore, seems fair to say, inasmuch as our experience was the same as that of most other investigators, that chronic cases respond to sulphanilamide somewhat more favorably than do acute cases.

It is important to note that the percentage of cures obtained by our Venereal Disease Research Laboratory in the first 100 cases was much higher than the 198 cases subsequently treated. This

can probably be accounted for by the fact that their dosage was considerably larger and continued for a longer time. Our 198 patients were chiefly treated by a definite routine, as will be explained later under the caption "Dosage."

2. *Time of the Disappearance of Discharge.* There is general unanimity regarding the fact that in successful cases the urethral discharge disappears within 5 days of commencing a course of sulphanilamide. In our successful cases, the average time for the cessation of the discharge in the acute cases was 4.9 days, for the chronic 4.3 days.

3. *Period of Hospital Stay.* There is also unanimity regarding the diminution of the period of symptoms and the consequent necessity for medical care. Crean states, "It has reduced the days of sickness to one-third." The hospital stay for our successful cases averaged 15 days whether acute or chronic, and for our failures, 49 days for the acute and 45 days for the chronic cases. Of course, 15 days was generally longer than was absolutely necessary in the successful cases. Many patients were, or could have been, discharged in 10 or even 7 days.

4. *Criteria of Cure.* Johnson and Pepper: Those patients who 10 or more days after the beginning of the treatment had a positive smear or culture, or showed a hazy or cloudy urine in one or both glasses, are classified as failures.

Reuter: "Disappearance of microscopic pus from the urine, absence of pus from the prostate, loss of all symptoms and failure to produce a recurrence."

Orr: In the male: Absence of gross pus or shreds in 1st or 2d glasses, and by demonstration of less than 8 pus cells per oil immersion field in the prostatic fluid.

Crean: First day: Urethroscopy: Injection of gonococcus vaccine, 1 cc. subcutaneously (1 cc. contains 50 million). Injection of 5 cc. of a 1% solution of silver nitrate into anterior urethra. Microscopic examination and culture of any resultant discharge.

Second day: Examination of urine (2-glass test). Examination of prostate and seminal vesicles and microscopic examination of prostatic fluid. Passage of a Clutton's sound, and further examination and culture of any discharge noticed or obtainable the following day.

Van Slyke *et al.*: A moderately sized sound was passed into the bladder and the pendulous portion of the urethra massaged over the sound. If this procedure did not produce recurrence of the discharge, the maneuver was repeated on the following day. After the 2d sounding, the distal part of the penis was cleansed with soap and water, the prostate thoroughly massaged, and the combined urethral-prostatic secretion examined by smear and culture. If found to be negative, the entire procedure was repeated after a 2-day interval. For purposes of lubrication of the sounds, a sterile tragacanth jelly

free from preservatives was used. (It will be noted that this test of cure consumed 5 to 7 days.)

Our criteria: Disappearance of discharge and burning after one course of sulphanilamide (5 days), both glasses clear, smears negative for Gram-negative diplococci (even if extracellular) after the passage of two sounds, with prostatic massage after each, the second sound being passed 2 days after the first. A persistent morning drop, or a few fine shreds when both glasses were clear, or the presence of occasional pus cell in a scanty morning drop, were not construed as making the case a failure, if the other criteria of success were met with.

It is difficult to evaluate the standards of cure quoted. None of these standards is sufficiently trustworthy to guarantee positively against relapse or transmission of the disease; but, on the other hand, any one of them would probably have been considered adequate tests prior to the use of sulphanilamide. The authors believe that, in the great majority of cases that they have considered cured, relapse or transmission of the disease will not occur, but advise precautions against the possibility of transmission to sexual partners for 1 month, and advise alcoholic indulgence (if so inclined) as a test of relapse.

5. *Frequency of Relapses.* In Pepper and Johnson's series, in 15 of the cases in which the discharge stopped rapidly after the onset of treatment, a positive smear or culture was later obtained. In Crean's series of 68 acute cases, there were 2 relapses; 1 relapse of 24 chronic cases. In Knight's series, 10 of 63 out-patients and 5 of 60 in-patients had relapses. Herrold had 10 cures of 12 chronic patients, and followed the cured patients for 1 to 3 months, without evidence of infection. Van Slyke *et al.* told cured patients to return frequently for observation. Almost half of them (43) returned for observation at periods ranging from 15 to 134 days and now 9 months subsequent to discharge. None of this group has experienced a clinical or bacteriologic relapse. Practically all reported immediate return to hard work and indulgence in alcohol and sexual intercourse. Our total number of relapses is unknown, for the patients on discharge frequently ship to parts unknown.

It will be seen from the foregoing that a satisfactory clinical cure with sulphanilamide seems in the majority of cases to be a real bacteriologic cure, but that relapses sometimes will occur. This, however, does not detract greatly from the value of sulphanilamide therapy.

6. *Dosage.* Table 2 shows the dosage schemes followed by several authors. Crean's doses are not included, as he used both prontosil soluble and sulphanilamide simultaneously. It will be seen from the table that we have used the most intensive type of dosage of any series, and that subsequent to the series we are now reporting, we have started to use a still more intensive dosage. The

experimental work of Marshall *et al.*[19] has led us to the conclusion that it is wisest to give the drug at 4-hour intervals. Long and Bliss' work[17] tends to show that the mechanism of action is that of bacteriostasis (inhibition of bacterial growth). The concentration desired in the blood is given by different writers at different levels, but a fair average, according to Heterick,[12] is a 10 to 15 mg. per 100 cc. of blood, or 1 to 10,000 or 1 to 7500 concentration.

TABLE 2.—DOSAGE.

Author.	Grains for number of days.	Followed by grs. for No. of days.	Followed by grs. for No. of days.	Approx. total. grs.
Johnson and Pepper[13]	80 for 2–3	60 for 2–4	30–45 daily for maintenance	
Reuter[23]	40 daily (undeterminate period)			
Orr[21]	80 for 4	40 for 4	20 for 7	640
Knight[14]	80 for 3	60 for 3 Repeated if necessary	40 for 4	580
Ferguson *et al.* (in this series)	120 for 2 (except for 1st 100 cases treated by Van Slyke dosage)	60 for 3 Repeated if necessary	...	420
Ferguson *et al.* (now)	120 for 4	60 for 3 Repeated if necessary	...	660

Marshall *et al.*[19] plotted curves of blood concentration for different individuals after a single oral dose of sulphanilamide. In his Subject "c," whose curve appears to be an approximate mean of the others, the blood concentration of sulphanilamide reached 7.5 mg. % in 2 hours, and declined to 5 mg. % in 9 hours, after a single oral dose of 50 grains (3.6 gm., .05 gm. per kilo, subject's weight about 155 pounds). At the Venereal Disease Research Laboratory at Stapleton it was found that the administration of the drug at continuous 4-hour intervals seemed the correct method for the maintenance of an adequate concentration of sulphanilamide in the blood stream, and also that concentrations of from 8 to 10 mg. % of uncombined sulphanilamide were sufficient to produce apparent cures in some cases, but concentrations of from 10 to 15 mg. % appeared to be more efficacious. (There were failures at both levels, however).

For these reasons, we gave the drug to our 198 patients through the night as well as in the day, at continuous 4-hour intervals (making 6 doses in 24 hours), giving 120 grains a day for 2 days and then 60 grains a day (gr. x q 4 hours) for 3 days. The other 100 cases were given a dosage much higher than our series of 198 cases, but at the same intervals, every 4 hours (day and night), in accordance with Van Slyke outline. At present, however, we are giving 120 grains per day for 4 days, followed by 60 grains a day for 3 days, in an attempt to reach and maintain a concentration approaching 10 to

15 mg. %, mentioned above as seemingly more efficacious. This dosage (120 grains per day for 4 days, and 60 grains per day for 3 days) and even our former dosage (120 grains per day for 2 days, and 60 grains per day for 3 days) is larger and more intensive than those given by most other authors, but we do not feel that the toxic effects we encountered have rendered these amounts inadvisable. Some cases are continued on treatment for a longer period when well tolerated by the patient.

7. *Toxicity.* Severe and even fatal hemolytic anemias, granulocytopenias and other toxic reactions sometimes occur. However, we have had few serious, but rarely dangerous reactions. There were no hemolytic anemias observed. Workers at the Venereal Disease Research Laboratory failed, in their cases, to find evidence of sulphemoglobinemia or methemoglobinemia. Several of our patients had high fever, cutaneous eruptions, intense cyanosis, rapid pulse and general prostration, but all became well in 1 or more days upon discontinuance of the drug and forcing of fluids. Most of our patients showed some cyanosis and one or more toxic effects, like headache, dizziness, anorexia, lassitude, and insomnia, and often they lost about 5 pounds in weight, but these symptoms generally did not warrant cessation of the course of sulphanilamide. We instructed the nursing staff to withhold the drug whenever the temperature was above 38.2° C. We limited water intake to 1500 cc. a day. Inasmuch as a fall in the CO_2-combining power of the plasma to 38 to 45% was usual, we frequently gave sodium bicarbonate gr. xv t.i.d., to combat toxic symptoms. When laxatives were necessary, we used enemata or cascara sagrada.

Regarding cumulative effects, we have given several patients 2 to 4 courses of sulphanilamide, each course consisting of 420 grains or more in 5 days, over periods of about 6 weeks, with no ill effects. In fact, 1 patient had 1810 grains (122 gm.) in 31 days, without undue toxicity. This patient incidentally developed an acute epididymitis while under treatment.

Regarding precautions, we feel that hospitalization is strongly advisable.

The authors have been informed that other workers have given very large initial doses (120 grains as a first dose, for example), and subsequent relatively large single doses (as, 60 grains in 1 dose). While this type of dosage may, perhaps, prove valuable we feel that if certain of our patients who became toxic had been given these doses, fatalities might have resulted. We, therefore, feel it safer to proceed with 20 grain doses every 4 hours, especially because there is no urgent need to build up a high concentration within a matter of hours, as may indeed, be of vital importance in some virulent streptococcal or other toxin-producing infections.

8. *Value in Complicated Cases.* Herrold[11] treated 4 patients with epididymitis. The swelling and pain disappeared rapidly under

treatment. Reuter[23] had 2 cases arriving with epididymitis, and these subsided within 48 hours. Of 16 patients suffering with epididymitis 3 satisfied our criteria of cure as we treated them with sulphanilamide. The results in the complications of arthritis were indifferent.

9. Does Sulphanilamide reduce the *Incidence of Complications?* Johnson and Pepper[13] found the development of complications "less than in the routine out-patient treatment of this disease." Only 8 of 27 cases of anterior urethritis became posterior. Crean[6] found in his control series of 30 patients (27 acute, 3 chronic) treated with irrigations, that 10 of the 27 acute cases developed posterior urethritis, and 2 patients developed epididymitis. Reuter[23] had no case of epididymitis develop among his 100 treated cases. He says, "Those cases which did not improve, did not show any tendency to get worse, and remained stationary."

In our series of 298 patients, only a very small proportion of cases of anterior urethritis became posterior, and only 2 cases of epididymitis and 1 of periurethral abscess developed while under treatment.

10. *Should Local Treatment be Given Simultaneously With Sulphanilamide?* Erskine, Johnson and Lloyd reported early and marked improvement, with particularly excellent results when local treatment is used at the same time. In one-half of our patients, local treatment in the form of injections into the anterior urethra of 0.5% Protargol, t.i.d., was given simultaneously with sulphanilamide therapy. Table 3 summarizes our experience with simultaneous local treatment, and without it.

TABLE 3.—CASES WITH SIMULTANEOUS LOCAL TREATMENT AND SULPHANILAMIDE.

Acute.		Chronic.		Total (acute and chronic).	
Successes.	Failures.	Successes.	Failures.	Successes.	Failures.
64	35	25	10	89	45
64% success		71% success		66% success	

CASES WITHOUT LOCAL TREATMENT.

Acute.		Chronic.		Total (acute and chronic).	
Successes.	Failures.	Successes.	Failures.	Successes.	Failures.
89	22	48	5	137	27
80% success		90% success		83% success	

It will be seen that combined local and chemotherapy gave us 66% of cures, as compared with 83% of cures by chemotherapy alone.

11. *Comparison of Results in Those who Admit One or More Previous Gonorrheal Infections and in Those who Deny any Previous Infection.* Table 4 shows that of 43 patients denying gonorrhea there were 67% successes, while of 49 who admitted one or more previous attacks, there were 84% of cures with sulphanilamide. This seems to substantiate the opinion of Herrold[11] (with reference to acute cases), that the best results seem more probable in patients

who have previously had gonorrhea. This tends to imply that an immune mechanism plays some part.

TABLE 4.

PART A—DENYING PREVIOUS INFECTION.

Acute.		Chronic.		Total (acute and chronic).	
Successes.	Failures.	Successes.	Failures.	Successes.	Failures.
25	12	4	2	29	14
67% success		67% success		67% success	

PART B—ADMITTING PREVIOUS INFECTION.

Acute.		Chronic.		Total (acute and chronic).	
Successes.	Failures.	Successes.	Failures.	Successes.	Failures.
33	6	8	2	41	8
85% success		80% success		84% success	

PART C—EXCLUDING THE 17 CASES WHICH HAD SULPHANILAMIDE PRIOR TO ENTRY.

Denying previous infection.	Admitting previous infection.
Acute:	Acute:
20 of 25 patients, 80% success	32 of 36 patients, 89% success
Chronic:	Chronic:
4 of 5 patients, 80% success	8 of 9 patients, 89% success

(Figures in Part A include 17 patients who were given sulphanilamide before hospitalization, and so were not included in our results).

13. *Influence of Previous Inadequate Dosage of Sulphanilamide, on the Efficacy of Our Course of Sulphanilamide.* We found 14 patients in which sulphanilamide had been taken prior to our treatment. They had been given the drug by a ship's physician, druggist, and others. Arbitrarily considering doses of less than 60 grains for 5 days, or less than 40 grains for 10 days, as inadequate, and higher doses as "sufficient," we find among the inadequate dosages, 10 patients with 4 cures. From the fact that there were only 4 cures among the 10 previously given inadequate courses, whereas we would expect at least 7 cures among 10 cases who had none of the drug previously, one may surmise that previous inadequate dosage might diminish the chance of satisfactory response to a subsequent adequate course of the drug. This opinion has been expressed by other authors, and it is included here because it is, perhaps, plausible according to bacteriologic theory. If (speaking generally) a concentration of a chemical is attained which is not sufficient to check bacterial reproduction, the bacteria present can sometimes develop an adjustment or tolerance to that chemical, and subsequently continue to multiply even though the concentration is later raised to a higher level, at which their growth formerly would have been checked.

Once an adequate course of sulphanilamide has failed, a subsequent adequate course of the same drug is also likely to fail. This tends to be supported by the fact that the authors have had failures after a third or fourth course. When another treatment like typhoid vaccine or local treatment is interspersed between sulphanilamide a cure has been occasionally effected.

The possibility occurs that some closely related compound might

be found which would prove efficacious as an adjuvant to overcome the bacterial tolerance acquired for the sulphanilamide.

13. *Further Comments on the Problem of Failures.* Regarding the problem of failures, we had 55 patients whom we classified as failures after one course of sulphanilamide (consisting, as noted, of 120 grains a day for 2 days, and 60 grains a day for 3 days). Crean[6] expressed the opinion that a failure with sulphanilamide caused an adverse effect on the ability of the body to react favorably to other forms of treatment.

To continue on somewhat surer ground, in our 55 failures, a variety of other therapeutic measures was tried, including courses of intravenous typhoid vaccine, gonococcus vaccine or antitoxin, courses of anterior irrigations or injections, and hyperpyrexia. Gonococcus antitoxin was soon discontinued because of serum reactions. After a course of typhoid injections, another course of sulphanilamide was successful in some patients, but failed in others. Hyperpyrexia (the fever-box) was generally tried last, and was generally successful after one or more treatments. In connection with this, it is interesting to note that one author[2] found that a combination of sulphanilamide and hyperpyrexia simultaneously is more successful than either method alone. Hyperpyrexia is not practical for large numbers of patients but it may be that this combined method will prove valuable in rather resistant cases.

14. *Reasons for Failures.* The reason for the failures we do not know. Toxic reactions in some cases cause temporary withdrawal or permanent discontinuance of the drug, with consequent fall in blood concentration. This has apparently caused failure. Reuter[23] observed, however, that those patients who complain early and bitterly of the side-effects, gave the best response to treatment, while the cases which are counted as failures appear to have had a greater tolerance for the drug. This implies that the minor toxic effects are a manifestation of some form of body response to the drug, and that this body response exerts the curative action. The authors could not correlate the degree of minor toxic effects with the degree of success of treatment.

Insufficient amounts of the drug, or too short a time-period of its administration, are likely reasons for many failures. However, even when adequate courses are given, in both the successful and in the unsuccessful cases, the absorption, the maintenance of a satisfactory concentration in the blood stream, and the rapidity of elimination, were entirely comparable.[24]

A hypothetical bacterial tolerance to the drug, acquired as a result of previous inadequate dosage (and also adequate dosage in individuals who do not respond), may be postulated to account for some failures on subsequent adequate course of therapy.

Crean[6] observed that robust patients were more likely to be cured than underweight or anemic-looking patients. Our series of cases

do not seem to substantiate this statement, because we have noted cures and failures in both robust and underweight individuals.

Reuter,[23] in a statement already quoted (namely, "It was felt that perhaps these cases—which did not improve with sulphanilamide therapy, but remained stationary—were destined to be of that severe fulminating type,)" seems to us to imply that in some cases, the reason for failure may be an exalted virulence of the particular strain of invading gonococci.

Crean[6] states that the earlier in the infection the patient was started on prontosil-soluble and sulphanilamide, the greater was the chance of success.

15. *Mode of Action.* The question of the mechanism of action is unsettled, and constitutes a very important and interesting problem. Heterick,[12] gives a good résumé of the history of sulphanilamide, showing that Heidelberger and Jacobs* found in 1919 that para-sulphonamide benzene azo-compounds had bactericidal properties, that Domagk* in 1935 demonstrated positive protection for mice against hemolytic streptococci; that Nitti and Bovet performed similar experiments; that Nitti, Bovet and Trefouel produced a white crystalline organic compound which contained the benzene-sulphonamide group, minus the azo-linkage (sulphanilamide or "prontylin" type compound, as compared with "Prontosil"—type compounds, containing the azo-linkage). Horlein was of the opinion that the results depended on an activation of the reticulo-endothelial system; but that Levaditi and Vaisman hold an opposite view, that of an inactivation or inhibition of streptococcal hemolysin, which theory is supported by the work of Osgood and Brownlee.[22]

Long and Bliss[17] showed that a 1 to 10,000 concentration of sulphanilamide in serum broth markedly inhibited the growth of streptococci, pneumococci (Types I and II), but had no effect on *Staph. aureus*, for example. Cohn[5] showed that sulphanilamide in dilutions of 1 to 1000, to 1 to 100,000 exerted a bactericidal effect on gonococci *in vitro* when incubated 24 hours at 37.5° C. Levaditi and Vaisman[16] showed that sulphonamide-azo dye derivatives protected mice against intraperitoneal injections of gonococci, which otherwise gave rise to fatal peritonitis and sepsis. Mellon, Gross and Cooper's[20] experiments, according to Orr, showed no indication that phagocytosis is a factor in the mechanism of the therapeutic action in gonorrhea. Bigler *et al.*,[3] working with streptococci, concluded that the action of sulphanilamide seems to be independent of the leukocytes.

Summary. 1. Of 298 cases of gonorrheal urethritis in hospitalized males treated with sulphanilamide, 76% satisfied our criteria of cure.

2. In successful cases, the discharge and burning disappeared within 5 days of starting sulphanilamide, and the patients were discharged in 9 to 15 days after admission to the hospital.

* References can be found in Heterick's article.[12]

3. Of our acute cases, 73% were cured; of our chronic cases (over 28 days' duration), 83% were cured.

4. Sulphanilamide therapy in successful cases greatly reduces the time period for which medical treatment is necessary, as compared with the time generally necessary before the days of sulphanilamide.

5. Relatively few relapses after apparent cure with sulphanilamide have been reported in the literature, over follow-up periods generally less than 3 months.

6. We have used a relatively large and intensive method of dosage in our cases (all hospitalized), namely 120 grains a day for 2 days, followed by 60 grains a day for 3 days. We gave the drug at continuous 4-hour intervals, night and day. We now believe that 120 grains a day for 4 days, followed by 60 grains a day for 3 days, will prove to be more efficacious.

7. While severe and sometimes fatal toxic reactions doubtlessly occur, we have had only a few serious, and rarely a really dangerous reaction.

8. The drug is rapidly excreted. When administered in short intensive courses of not over 10 days, the danger to the blood forming system is probably slight. If continued over this time even in smaller amounts a real danger of poisoning undoubtedly exists.

9. The presence of a complication seems to lessen greatly the chance of a rapid cure of the urethritis.

10. Local treatment would not seem to be warranted simultaneously with sulphanilamide.

11. A somewhat greater proportion of successes results among those who admit previous gonorrhea, than among those who deny it.

12. Inadequate dosage, administered prior to an adequate dosage and course of sulphanilamide, seems to impede the action of the drug.

13. The reason for the failure of the drug in about one-fourth of the cases is unknown, but certain seemingly pertinent inferences have been drawn.

14. We believe sulphanilamide has bettered the treatment of gonorrhea, but that older forms of therapy will continue to have a definite rôle.

15. The toxic reactions to the drug are characterized by pallor, cyanosis, malaise, anorexia, headache, occasionally vomiting, fever, and erythematous, macular rashes most noticeable over the face and extremities. The idiosyncrasy of patients plays a part in these reactions. These symptoms are similar to those noted in aniline poisoning. Excretion is rapid and recovery prompt when the drug is discontinued and fluids administered.

16. Adequate dosage should be maintained during treatment. To accomplish this, hospitalization is essential to assure this dosage and to protect the patient from untoward reactions.

Sharp and Dohme's, and Winthrop's Brands of sulphanilamide were used in this series.

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THE SEARCH FOR MORE EFFECTIVE MORPHINE-LIKE ALKALOIDS.*

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This investigation, begun in 1929, has proceeded under the auspices of the Drug Addiction Committee of the National Research Council at the University of Virginia, at the University of Michigan and recently at a number of clinical centers through the coöperation of the United States Public Health Service. Some 47 individuals are or have been directly concerned in carrying out the work.

In the beginning, two routes were open, either of which might lead to the solution of our problem, the production of a non-addicting analgesic. One of these was operation upon the alkaloids of promising structural type, especially those of the morphine group; the other was syntheses starting with unrelated or distantly related nuclei. The first path, while likely to lead to active drugs, had the disadvantage or attendant uncertainty of whether or not products derived from morphine greater than or comparable to it in analgesic power might be likewise addicting. The second route had the obvious disadvantage that the possible starting materials and the directions in which synthesis might be undertaken were multitudinous and there appeared to be no previous experience in this connection beyond isolated haphazard experiments. However, both paths have been followed assiduously and we will endeavor to describe some of the stations which have been passed along the way.

Coincident with the development of the analgesic effect of mor-

* Read by invitation at the joint session of the Federation of American Societies for Experimental Biology, at Baltimore, March 31, 1938.

phine there occur other, often medically undesirable, actions in the body, namely its respiratory, circulatory, gastro-intestinal, emetic, convulsant, and general depressant manifestations. We are obliged to speak of both the convulsant and general depressant actions of morphine because its effect is diphasic in all species though not equally so. An outstanding difference in the action of morphine in man and animals is the preponderance of convulsant action in many of the latter and of depression, especially of the respiratory mechanism, in the former. In addition, the administration of morphine to man, at least in many individuals, not only relieves the discomfort of pain and restlessness but also causes a pleasurable feeling of well-being, a "euphoria." Both the relief of discomfort and the euphoria may lead to repeated administration and repeated administration sooner or later leads to dependence, the *sine qua non* of addiction. Dependence is demonstrably physical as well as mental and it is our belief that there is a relationship between it and the chemical structure of the addicting agent of the morphine series just as probably as that there is a relation between chemical structure and the analgesic or any other property of the drug. The relationship, of course, may be either to the nuclear skeleton of morphine or to the presence of certain modifiable peripheral groups. We propose to show that modification of the latter may not uniformly modify the morphine picture which is presumptive evidence of a relation between the actions of morphine and the peripheral groups, and we submit that each successful demonstration of dissociation by chemical means between any of the properties of morphine adds to the hope of eventual dissociation of the analgesic and addicting factors.

The work itself on this project started and our description can also start most simply with the chemical modification exemplified in the naturally occurring alkaloid, codeine, which differs from morphine only in the presence of an OCH_3 group replacing a phenolic OH (Fig. 1). It is well known that codeine is weaker than morphine in analgesic, respiratory, depressant, emetic and intestinal effects. Clinical evidence indicates that it is less addicting than morphine, though there are no quantitative data available on the degree to which the addiction factor is reduced. On the other hand, in animals codeine has a much greater convulsant action and is more toxic.

If morphine is treated with reagents suited to replace the alcoholic hydroxyl by chlorine, such as phosphorus trichloride or thionyl chloride, isomeric chloromorphides are formed. Hydrolysis of either of these halogenomorphides with dilute acetic acid yields in varying amounts three isomers of morphine. Similarly we can prepare by halogenation and hydrolysis three isomers of codeine or these may be obtained by direct methylation of the morphine isomers.

The isomerism depends upon the position of the alcoholic hydroxyl, so that we have pairs of structural isomers of morphine and of codeine as the hydroxyl shifts from the 6- to the 8- carbon and pairs of diastereomers, whether the hydroxyl is on the 6- or the 8- carbon. Further, in each instance the alicyclic unsaturated linkage (between carbons 7 and 8 or between carbons 6 and 7) can be removed by controlled hydrogenation (Fig. 2). In this and the succeeding figures (Figs. 2 to 11) the structural formula of the parent substance (morphine in the present instance) is shown and, underneath, that portion only of the molecule is reproduced which has undergone the chemical change under consideration. In addition, in Figure 2 the isomeric configurations are indicated by reproduction of the portion of the molecule in which they occur. The substances thus represented (from left to right, upper row first)

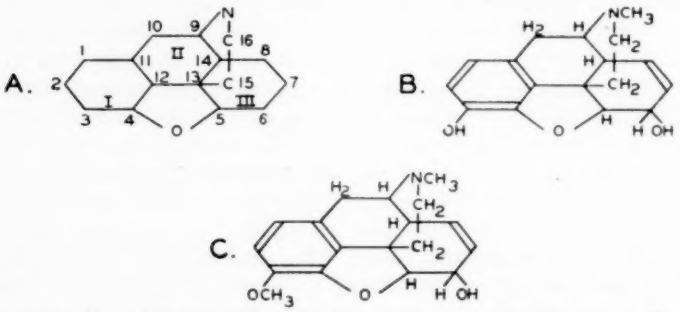


FIG. 1.—*A*, Morphine nucleus and numbering system. *B*, Morphine. *C*, Codeine.

are morphine, dihydromorphine, α-isomorphine, dihydro-α-isomorphine, β-isomorphine, dihydro-β-isomorphine, γ-isomorphine and dihydro-γ-isomorphine.* The isomeric configurations of codeine, dihydrocodeine and their isomers are identical and the codeine analogs in the order of the morphine series just enumerated are codeine, dihydrocodeine, isocodeine, dihydroisocodeine, allopseudocodeine, dihydroallopseudocodeine, pseudocodeine, and dihydropseudocodeine. We have then eight compounds, morphine, dihydromorphine and their isomers, differing from eight others, codeine, dihydrocodeine and their isomers, simply and only as morphine and codeine differ. If we compare these two groups serially we have an eightfold confirmation, or otherwise, of the typical difference exhibited in the change from morphine to codeine (Fig. 2).

The basis of comparison is the difference in effective doses expressed as a percentage of the greater dose. For example, the average fatal dose of morphine is 531, of codeine 241 mg. per kg., the difference is 290 or 54% of the greater dose. The toxicity of codeine

* All of the substances studied in this research were prepared at the University of Virginia by Lyndon F. Small, Erich Mosettig and their collaborators.

in relation to that of morphine then may be expressed as increased 54%. Again the respiratory minimal effective dose of morphine is 0.15, of codeine 1.30 mg. per kg. The difference is 1.15 or 88% of the greater dose, in this case the codeine dose, so that the respiratory effect of codeine in relation to that of morphine may be expressed as decreased 88%. In other words, where the line extends upward on the + side of the zero abscissa the codeine or derivative member of the pair is the more effective; where it extends downward the derivative member is the less effective, and the length of the line is related to the degree of difference. This explanation of the method of comparison applies also to Figures 3 to 11.

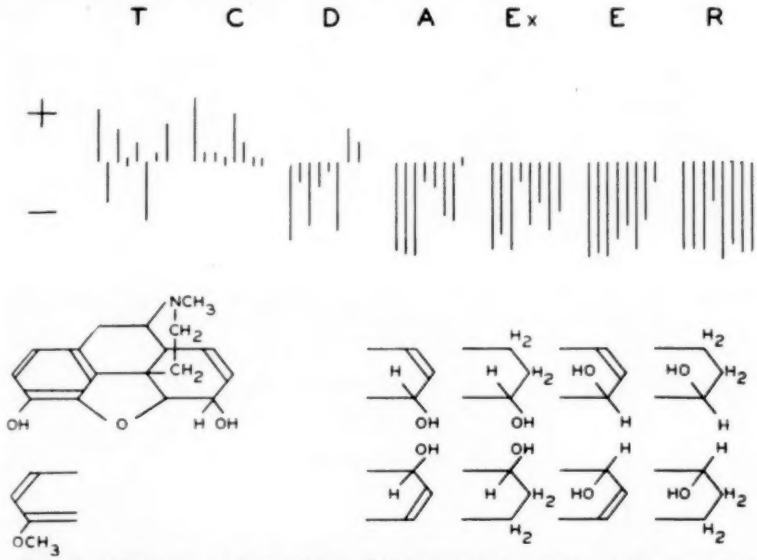


FIG. 2.—Comparison of morphine, dihydromorphine and their isomers with codeine, dihydrocodeine and their isomers; the effect of methylation of the phenolic hydroxyl. The initials at the top of the 7 columns indicate: toxicity (*T*), convulsant (*C*), general depressant (*D*), analgesic (*A*), exciting (*Ex*), emetic (*E*) and respiratory (*R*) effects. Each vertical line indicates the relationship in a single pair and the order is the same for each effect—morphine-codeine first, dihydromorphine-dihydrocodeine second, α-isomorphine-isocodeine third, and so on.

In this series of morphine and codeine isomers then the codeine-like difference is well borne out, toxicity and convulsant action are usually increased, other effects are decreased by methylation of the phenolic hydroxyl. The same result is obtained if we methylate similarly other morphine derivatives, the alcoholic ethers and esters and the desoxymorphines, for example. Methylation of the halogenomorphides, however, decreases toxicity and convulsant action as well as the other effects (Fig. 3).

To determine whether we are dealing with an effect of inactivation of the phenolic hydroxyl or of the addition of a methyl group

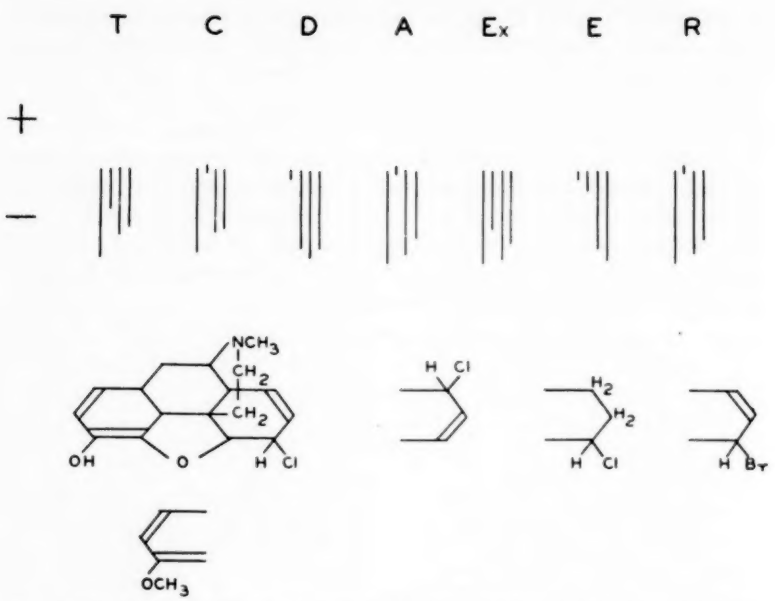


FIG. 3.—The effect of methylation of the phenolic hydroxyl of α-chloromorphide β-chloromorphide, dihydrochloromorphide and bromomorphide.

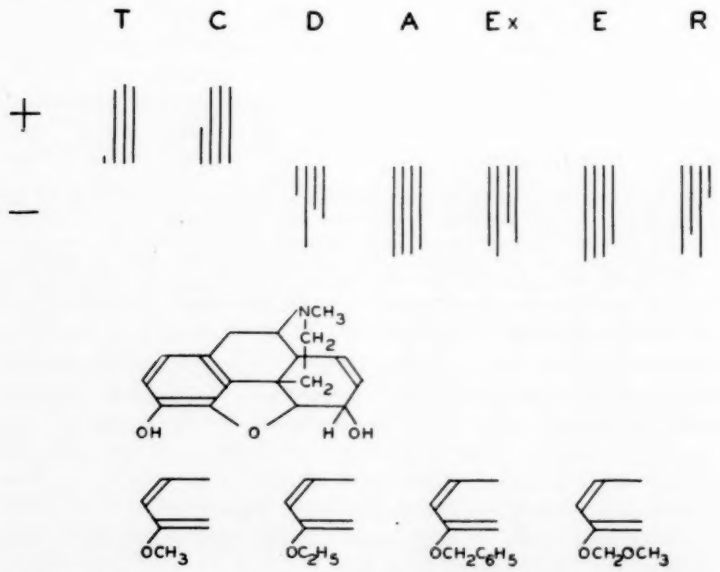


FIG. 4.—The effect of muzzling the phenolic hydroxyl of morphine and dihydromorphine with different groups—methyl-, ethyl-, benzyl-, and methoxymethyl-.

the phenolic hydroxyl can be muzzled by other groups in morphine and some of its derivatives. In Figure 4 the first line under toxicity, convulsant action, and so on, represents the difference in effect brought about by methylation of morphine and dihydromorphine, the second line the difference when the muzzling group is ethyl, the third line the difference when the muzzling group is benzyl and the fourth when the muzzling group is methoxymethyl. The latter two groups were selected because of a difference in the ease with which they are removable by hydrolysis. There are some details suggestive of specific differences, but in the main the four muzzling groups have the same effect. In the main also this change has been

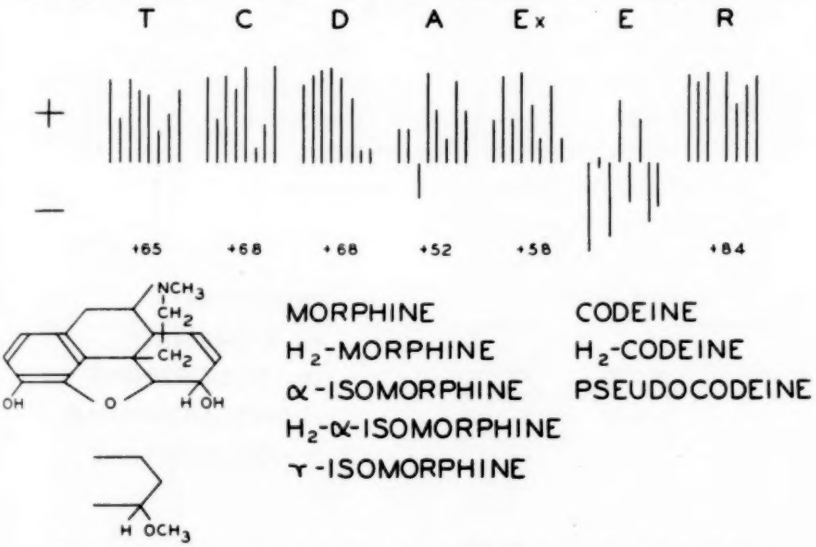


FIG. 5.—The effect of methylation of the alcoholic hydroxyl of the substances listed. Each figure below the graph is the composite percentage difference in effect for the group compared.

disadvantageous because even though we may show a reduction in addiction liability in the codeine analogs; that is, in the muzzled compounds, the reduction in other effects is too great for practical usefulness.

Another indication of the non-specificity of the addition of a methyl group can be derived from its use to muzzle the alcoholic hydroxyl of morphine and its derivatives (Fig. 5). Here the picture is quite different—effectiveness in most instances, including toxicity, is definitely increased. There are two points worthy of particular mention because of their bearing on our general thesis, namely, the variable change in emetic action whatever the effect in other respects, and the quantitative difference in analgesia and respiratory effect. The former is increased less (52%), the latter to a significantly greater extent (84%) than the change in toxicity (65%).

Many other changes have been effected in the alcoholic hydroxyl. Ethyl substitution (Fig. 6) gives a result very like that of methyl substitution, qualitatively and quantitatively. Note again the variable change in emetic effect and the quantitative difference in analgesia (average increase 38%), respiratory effect (average increase 91%) and toxicity (average increase 69%). The results of acetyl substitution (Fig. 7) are more irregular, possibly because of the ease with which the acetyl group may be removed by hydrolysis. Changing the hydroxyl to a ketone (Fig. 8) has an effect like that of alkylation. The same can be said of removal of the hydroxyl

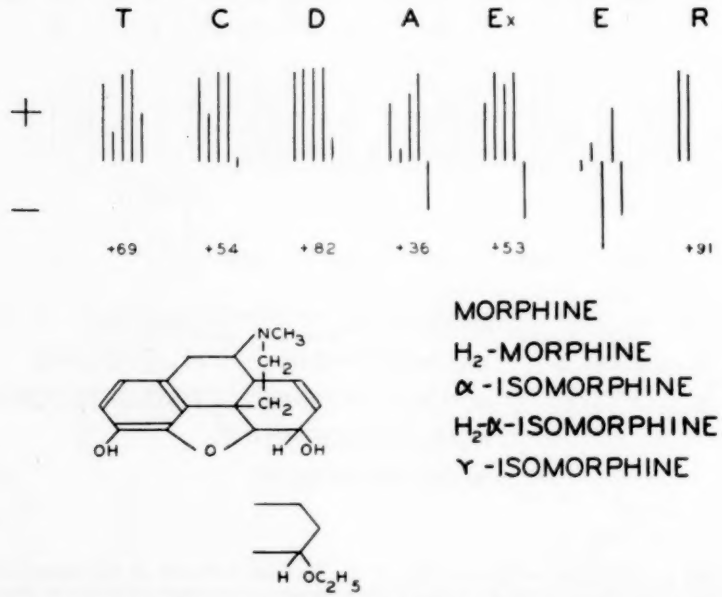


FIG. 6.—The effect of ethyl substitution of the alcoholic hydroxyl of the substances listed.

and its substitution by hydrogen (Fig. 9). This last change produces the greatest and most uniform increase in both depressant and analgesic effects though it also tends to shorten the duration of action. Halogenation, on the other hand (Fig. 10), is irregular in its effect, increasing the useful properties other than depressant action relatively little.

In sharp contrast to all of these modifications of the alcoholic hydroxyl is the effect of its replacement by a basic group (Fig. 11). These groups were tried because of the results obtained with simple phenanthrene amino alcohols, and it is disappointing to find that toxicity and all morphine-like effects are decreased markedly whether the basic group is diethylamino- or piperidino-.

A different type of morphine derivative is produced by the addition of a new nuclear substituent (Fig. 12). For example, in 2-aminomorphine a basic amino group has been introduced at carbon

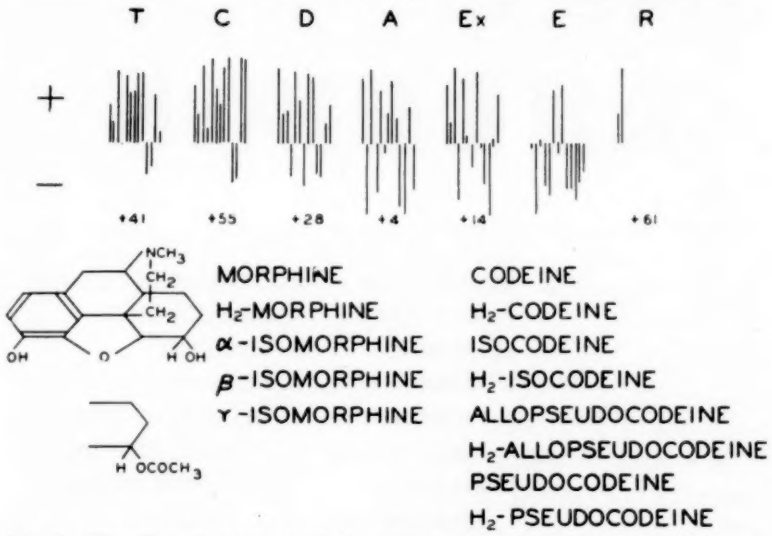


FIG. 7.—The effect of acetyl substitution of the alcoholic hydroxyl of the substances listed.

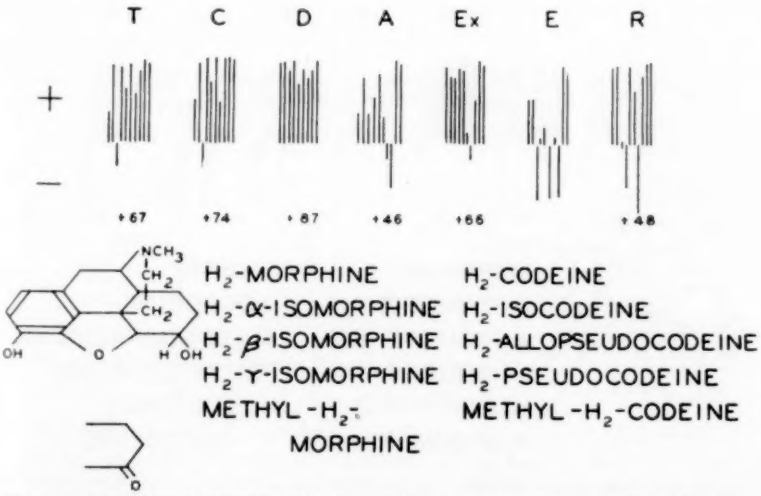


FIG. 8.—The effect of changing the alcoholic hydroxyl to a ketone in the substances listed.

-2 and in the hydroxycodeines and hydroxycodeinones a hydroxyl group at carbon -14. In each of these instances the morphine-like properties are decreased in the new compounds.

Recently nuclear substitution has been accomplished also in the alicyclic ring of the morphine molecule either at carbon -7 or carbon -5. This group of derivatives and the method of preparation are

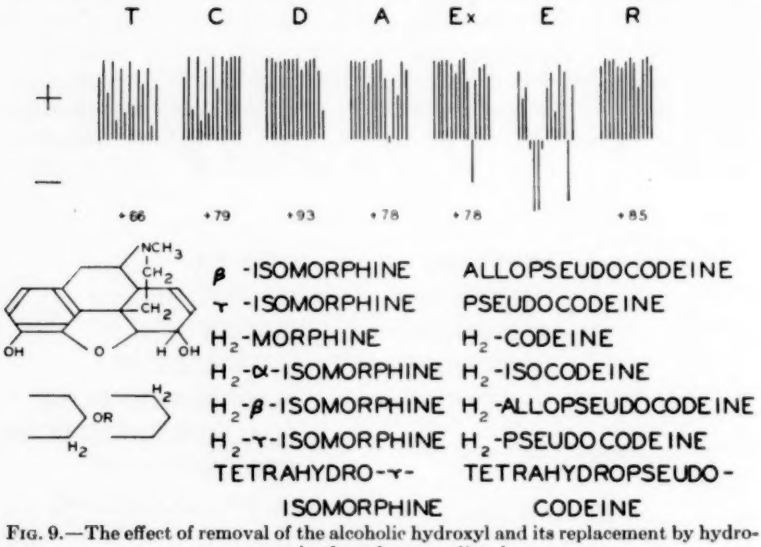


FIG. 9.—The effect of removal of the alcoholic hydroxyl and its replacement by hydrogen in the substances listed.

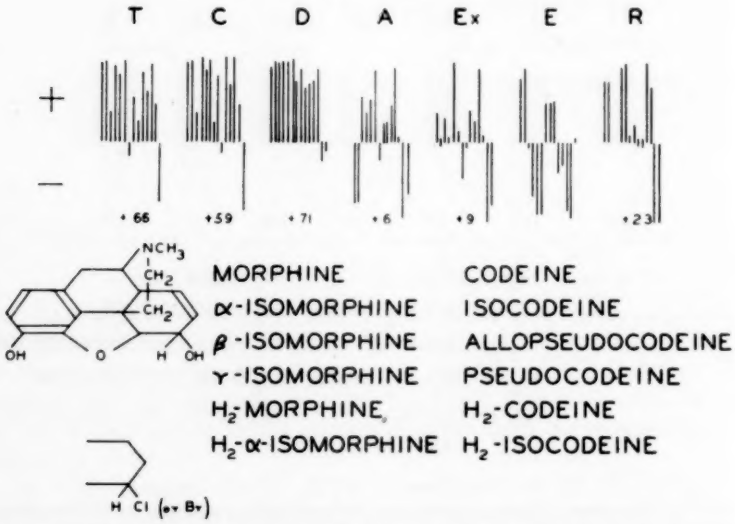


FIG. 10.—The effect of replacement of the alcoholic hydroxyl of the substances listed by chlorine or bromine.

entirely new. Thebaine, the naturally occurring alkaloid which is practically a waste product of morphine manufacture, is the start-

ing material and through a series of steps an alkyl derivative of morphine or codeine or any of their derivatives is possible. Examples are methyldihydromorphine and methyldihydrocodeine both of which are not convulsant, are less toxic and generally less effective than dihydromorphine and dihydrocodeine, respectively.

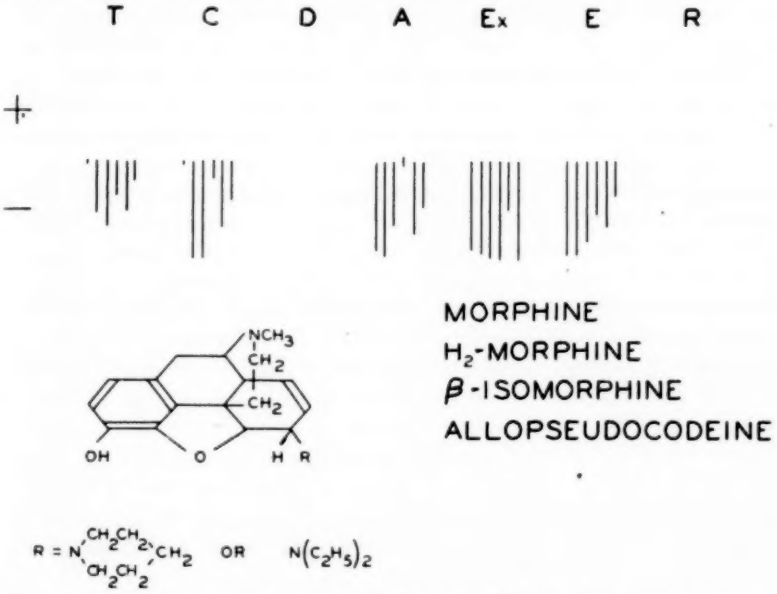


FIG. 11.—The effect of replacement of the alcoholic hydroxyl by a basic group—piperidino- or diethylamino-.

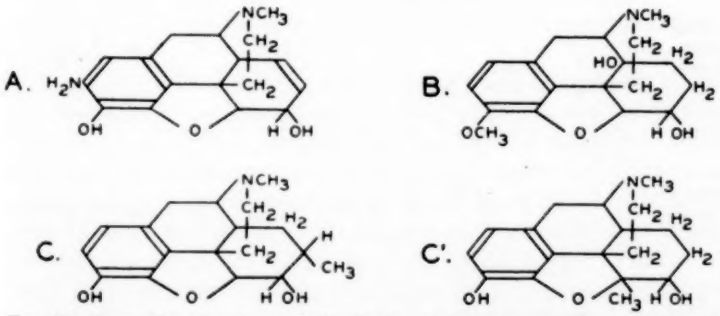
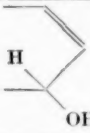
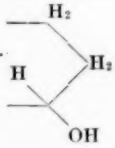
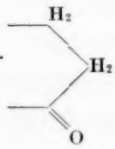
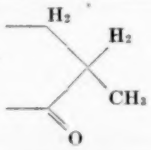
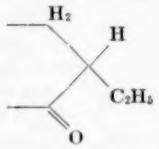
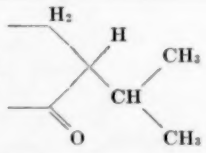
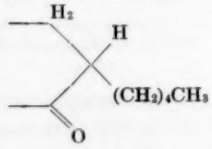


FIG. 12.—Examples of nuclear substitutions: *A*, 2-Aminomorphine. *B*, Dihydrohydroxycodeine. *C*, *C'*, Methyldihydromorphine. (Either configuration is possible).

The alkyl derivatives of this type of dihydromorphinone constitute a very interesting series. Of these methyldihydromorphinone is most promising and is being subjected to clinical trial. In man, it is twice as effective as an analgesic with a duration of action

TABLE 1.—MINIMAL EFFECTIVE DOSES IN ANIMALS.

	Modification from morphine molecule.	Toxicity.	Convulsant.	Depressant.	Analgesic.	Exciting.	Emetic.	Respiratory.
Morphine		531	531	6.75	0.75	0.57	0.22	0.15
Dihydromorphine		133	133	17.70	0.26	1.77	0.17	0.11
Dihydromorphinone		84	67	1.77	0.17	0.17	0.08	0.011
Methyldihydromorphinone		25	25	3.00	0.07	0.10	0.07	0.012
Ethyldihydromorphinone		27	22	2.01	0.17	0.09	0.17	0.021
Isopropyldihydromorphinone		17	13	2.25	1.33	0.26	1.80	0.10
Amyldihydromorphinone		11	5	0.22	0.36	0.04	0.36	0.002

approximately as great as morphine. No emetic action has appeared and no sign of respiratory depression in a large series of cases. In substitution studies in human addicts it has a very brief duration of dependence satisfaction possibly suggestive of a low addiction liability. The work with this substance in man is being extended in order to determine definitely its safety in respect to tolerance and addiction.

Before we leave this group note the quantitative and directional differences which have developed (Table 1). The figures in the table are minimal effective doses in animals and they present some very excellent examples of dissociation of morphine-like properties. Note, for example, that dihydromorphinone is more effective than dihydromorphine all the way along the line, while methyldihydromorphinone is more effective in respect to analgesia and excitement, not materially different in respiratory effect, but definitely less depressant. With isopropyldihydromorphinone in comparison with dihydromorphinone there is a marked difference in the change in analgesic and exciting effects—the former decreased from 0.17 to 1.33 mg. per kg., the latter only from 0.17 to 0.26 mg. per kg. In addition, the respiratory effect of the isopropyl derivative shows a tenfold decrease, from 0.011 to 0.10 mg. per kg. while depressant action is decreased only from 1.77 to 2.25 mg. per kg. Note also that analgesic and exciting actions are modified strikingly in opposite directions in amyldihydromorphinone—the former is decreased from 0.17 to 0.36 mg. per kg., and the latter is increased from 0.17 to 0.04 mg. per kg. Amyldihydromorphinone is the most toxic member of the group and is very markedly depressant to respiratory activity. It is also noteworthy that it is the only substance in this series, the depressant dose of which is less than that for analgesia.

In respect to the other possible route toward our goal, there are two important considerations. First, if the morphine picture is dependent upon the peripheral groups of the morphine molecule and the phenanthrene nucleus is just a carrier for these groups, then starting with phenanthrene it would seem possible by addition of suitable groups to bring out features of the morphine picture and we hope the analgesic feature to the greatest degree. On the other hand, if the morphine picture is inherent in the phenanthrene nucleus and the outlying groups are only handles or keys permitting its development, then the sort of analgesic that we want free from addiction liability will not be found in a phenanthrene derivative and we must rather try to build up a compound with a different nuclear structure. Having in mind both of these considerations our synthetic route has become a number of parallel roads along which

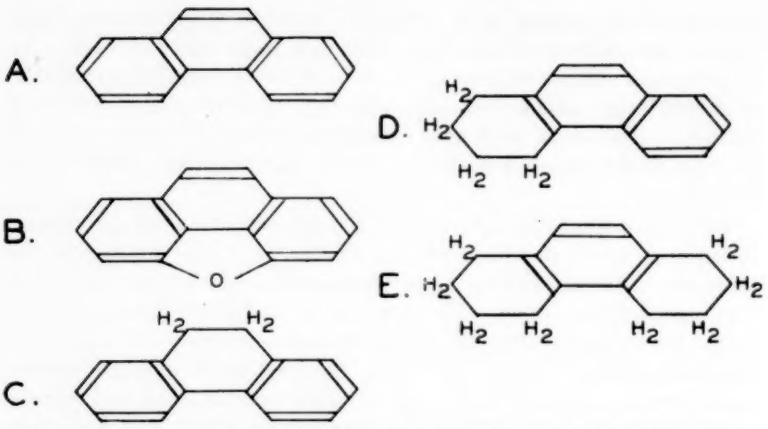


FIG. 13.—*A*, Phenanthrene; *B*, phenanthrylene oxide; *C*, 9, 10-dihydrophenanthrene; *D*, 1, 2, 3, 4-tetrahydrophenanthrene; *E*, 1, 2, 3, 4, 5, 6, 7, 8-octahydrophenanthrene.

$$OH \rightarrow OCH_3 \rightarrow OC_2H_5 \rightarrow OCOCH_3$$

$$COOH \rightarrow CH_2COOH \rightarrow COOCH_3 \rightarrow$$
$$CONH_2 \rightarrow CON(CH_3)_2$$

$$CHO \rightarrow COCH_3 \rightarrow COCH_2CH_3$$

$$CHOH \rightarrow CHOHCH_3$$

$$NH_2 \rightarrow NHCH_3 \rightarrow N(CH_3)_2$$

$$CH_2NH_2$$

$$CH_2CH_2NH_2$$

$$COCH_2NR_2$$

$$CHOHCH_2NR_2$$

$$CHOHCH(CH_3)NR_2$$

$$CHOHCH_2CH_2NR_2$$

$$OH \cdot OH$$

$$OH \cdot NH_2 \rightarrow OH \cdot NR_2$$

$R =$ $-H_2$, $-CH_3$, $-C_2H_5$, $CH_2CH_2\diagdown\diagup CH_2$ (CH_2CH_2), and

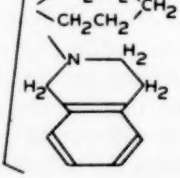
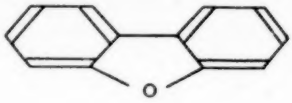


FIG. 14.—Some of the substituents which have been added to phenanthrene and to a lesser extent to the other nuclei of Fig. 13.

we progress as rapidly as the difficulties of syntheses will permit. The phenanthrene road itself has a number of parallel lanes according to whether the starting material is phenanthrene, a partially hydrogenated phenanthrene or phenanthrylene oxide. Figure 13



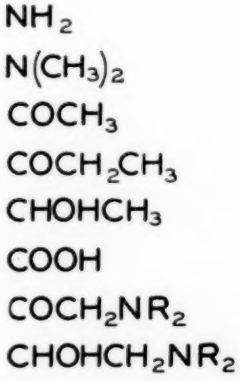


FIG. 15.—Dibenzofuran and some of the substituents which have been added to it.

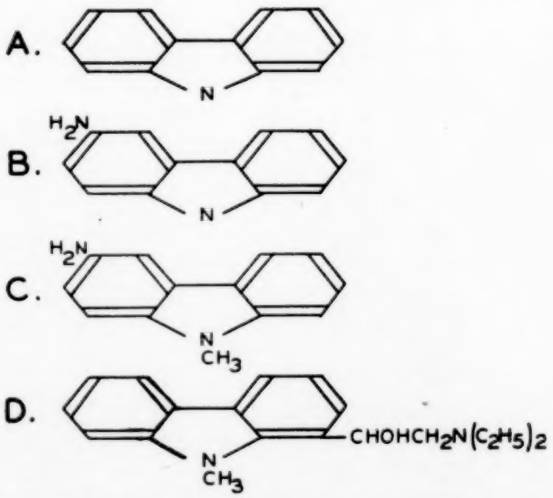


FIG. 16.—*A*, Carbazol; *B*, 3-aminocarbazol; *C*, 3-amino-9-methylcarbazol; *D*, 9-methyl-2-[1-hydroxy-3-diethylamino]-propyl carbazol.

shows these simple nuclei and Figure 14 some of the substituents which have been added to phenanthrene and to a lesser extent to hydrogenated phenanthrenes and phenanthrylene oxide.

The two other most important highways which have been travelled so far start from dibenzofuran and carbazol. The former differs from phenanthrene in having only two 6-carbon rings but it has an oxygen bridge as in phenanthrylene oxide. Carbazol is similar to dibenzofuran in having only two 6-carbon rings; it has a third ring closed by a nitrogen bridge. Figure 15 shows a few of the substituents which have been added to dibenzofuran, and Figure 16, carbazol and some of its derivatives. From examination of nearly 200 compounds synthesized for this phase of the work, most of them new, certain conclusions can be drawn.

Of the simple nuclei without substituents phenanthrene, octahydrophenanthrene, dibenzofuran and carbazol are nearly inert. 9, 10-Dihydrophenanthrene and tetrahydrophenanthrene are more effective, that is, more depressant when administered to animals. Derivatives of 9, 10-dihydrophenanthrene, however, are highly emetic and often convulsant. The addition of simple substituents to the nuclei increases their effectiveness and may even cause the appearance of some analgesic action. Increasing the length and complexity of the side chain up to a certain extent at least increases activity. It seems especially desirable to have a tertiary nitrogen in the side chain and a hydroxyl group attached to the nucleus or in the side chain. Of analogous dibenzofuran and phenanthrene derivatives the former are the more analgesic but also the more toxic.

The most effectively analgesic phenanthrene derivative that we have found so far is one derived from tetrahydrophenanthrene with a hydroxyl attached to the nucleus together with a tetrahydroisoquinoline group (Fig. 17). It is definitely analgesic and depressant in cats with a dose as small as 15 mg. per kg. but has not developed other typical morphine-like actions. Its homolog (Fig. 18) in which a CH_2 intervenes between the phenanthrene and tetrahydroisoquinoline is not more analgesic but even in small dose produces typical morphine-like excitement in cats. It also dilates the pupils and increases the heart rate, but is not convulsant and only very slightly emetic. The isomer of this homolog in which the side chain is on carbon -2 is inactive.

The carbazol derivatives are probably the most promising of our synthetic substances exhibiting a high degree of analgesic and depressant effects with low toxicity and usually little emetic action. The most active member is an amino alcohol derivative (Fig. 16, *D*), the effective dose of which is only 10 mg. per kg. It is not morphine-

like in other respects. The carbazols in general lower the temperature and are apt to produce considerable incoördination, besides being occasionally emetic. If we can find the means of avoiding these side actions and effect a little greater increase in analgesic action this group offers considerable hope of a useful clinical substance for which there is no reason to anticipate addiction liability.

In conclusion, very brief reference should be made to the clinical studies which are going forward in connection with this work.

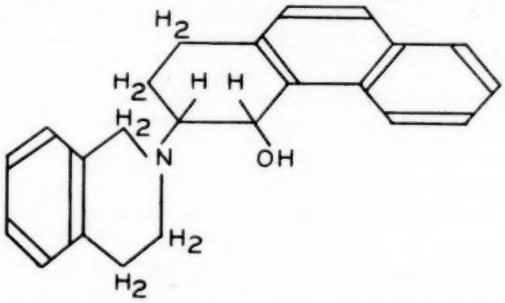


FIG. 17.—3-py-Tetrahydroisoquinolino-4-hydroxy-1, 2, 3, 4-tetrahydrophenanthrene.

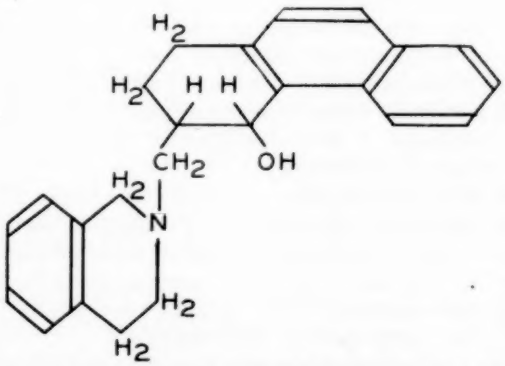


FIG. 18.—3-[(Tetrahydroisoquinolino)-methyl]-4-hydroxy-1, 2, 3, 4-tetrahydrophenanthrene.

Clinical facilities have been made available at a number of places in order that the pharmacologic studies may be extended to man. These facilities will permit the determination of effectiveness for clinical relief of pain and cough, the existence or otherwise of side effects, the effect of prolonged administration to non-addicts and the effect of selected substances on morphine addicts particularly in terms of dependence satisfaction. A score of substances have so far been submitted to some degree of clinical trial and of these the most promising is methyldihydromorphinone.

MASSIVE DOSE ARSENOTHERAPY OF SYPHILIS BY THE INTRAVENOUS DRIP METHOD: FIVE-YEAR OBSERVATIONS.*

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The method of the slow intravenous drip has made possible the safe introduction of drugs in amounts far exceeding our previous conception of dosage.[3,4a] The chemotherapy of early syphilis offered a clinical proving ground for the testing of this basic therapeutic principle. The technique of the intravenous drip and the preparation of solutions and materials have been the subjects of previous communications.[4b,5] The application of the drip method to the therapy of early syphilis has made possible the safe introduction of arsphenamine in doses sufficiently great to approach the "sterilisatio magna" of Ehrlich.[2]

Clinical Material and Dosage. In a previous paper, 25 otherwise healthy male patients, suffering from primary or early secondary syphilis, were treated with massive doses of neoarsphenamine by the intravenous drip method. The immediate and specific effects on the luetic lesion, the immediate toxic effects, particularly the fevers, toxicodermia and polyneuritis were described.[1] A total approximating 100 gm. of neoarsphenamine was given over a span of time that averaged less than 5 days. The smallest amount of neoarsphenamine injected was 2.4 gm.; the largest amount 5 gm.; and the average dose 4 gm. The majority of patients were treated over the course of 4 days, the longest duration of time was 6 days.

Late Toxic Sequalæ. None of the late parenchymatous lesions that may follow the exhibition of the heavy metals was experienced in any of the patients. Neither was there any evidence of jaundice, or liver damage, or any of the serious exfoliative skin lesions.

* This report is No. VI in the *Studies of Velocity and the Response to Intravenous Injections*, and emanates from the Department of Medicine, Service of Dr. George Baehr; Department of Dermatology, Service of Dr. Isadore Rosen; the Mount Sinai Hospital, and the Division of Venereal Disease, Department of Health, New York City.

Clinical Course. The clinical course of our patients during the 5 years that have elapsed since therapy was begun has been exceedingly difficult to follow. It has seemed wisest to present the data rather than statistics or conclusions. Five patients (Cases 5, 6, 10, 13, and 24) disappeared from observation before they achieved seronegativity. Two of these disappeared before 1 month had elapsed, 1 before the second month, 1 before the third month, and 1 before the fifth month of observation. The last named (Case 6) unfortunately, received only 2.9 gm. of neoarsphenamine, an amount which we now believe to be insufficient in the massive treatment of early syphilis.

A second group of 5 patients (Cases 9, 12, 15, 16, and 21) achieved seronegativity, but were not followed a sufficient length of time for satisfactory observation. In particular, 1 of these patients (Case 15) maintained a 4+ Wassermann for 11 months and had only 1 negative Wassermann at the end of the twelfth month, though he received the full course of 5 gm. of neoarsphenamine. Of the others in this group, 2 disappeared from observation in the second month, 1 in the fourth month, and 1 in the eighth month.

Of the remaining 15 patients, we have repeated negative blood Wassermann tests in 11, sufficient for us to feel certain that their late clinical course has been wholly and completely uneventful. No one of these patients received any other therapy of any nature whatsoever during this time. We have spinal fluid findings on 13 of the group: 5 made at the end of a year, 1 at the end of 2 years, and the remaining 7 made at the end of 5 years—all of which are completely negative so far as serology, cell count and globulin reactions are concerned, with the possible single exception to be detailed later. There are 9 normal teleoroentgenograms in this same group, one made at the end of 4, and the others at the end of 5 years of observation.

Four patients in this group require explanatory notes: One man (Case 25) who was 4+ on admission and at the end of the first month of observation, was not seen again for $4\frac{1}{2}$ years, at the end of which time he had a negative blood Wassermann, negative spinal fluid, and a normal teleoroentgenogram. A second member of this group (Case 22) disappeared from our observation when he was discharged from the hospital and was not seen by us until 54 months had elapsed, at which time his Wassermann, spinal fluid, and teleoroentgenogram were normal. This patient, a hospital orderly, continued the therapy of his case without our supervision. He reports that his Wassermann was negative 6 months after discharge from the hospital, by which time he had already received 12 injections of mercury. Because of his knowledge of the disease he insisted upon receiving therapy wherever he went and, to date, he has received another 27 injections of mercury. He had repeated Wassermann tests done at various institutions including Welfare Island, the

Hospital for Joint Diseases, and the New York Hospital. On one occasion, in 1935, his blood Wassermann and spinal fluid were simultaneously reported to be 2+, both tests being done at the same time. Thereafter, however, and at all of the other institutions his Wassermann and spinal fluid have been persistently negative, the succeeding spinal fluids being done 3 months and 3 years respectively after the one reported positive. Whether this one blot on his escutcheon represents a true recrudescence or a technical error, cannot be stated but it is only fair to point out that it would be exceedingly unusual for a recrudescence to be so transitory.

CHART 1.—CLINICAL DATA.

Case number.	Initials.	Hospital number.	Primary lesion.	Dark-field examination.	Secondary eruption.	Miscellaneous.	Date of admission, 1933.	Duration of treatment in days.	Total neoarsphenamine injected in grams.
1	D. M.	352,575	○	○	+	.....	May	4	2.4
2	W. S.	352,817	○	○	+	Iridocyclitis	June	4	2.9
3	G. S.	357,027	+	○	+	.....	June	4	3.5
4	L. S.	353,445	+	+	○	Primary of lip	June	4	3.3
5	W. C.	353,639	+	○	○	.....	June	4½	3.2
6	O. S.	353,819	+	○	○	.....	June	4	2.9
7	J. S.	372,747	+	+	○	.....	July	5	4.0
8	J. C.	369,104	○	○	+	.....	July	5	4.6
9	A. S.	355,089	+	+	○	Primary of lip	July	5	4.7
10	J. D.	355,194	+	○	+	.....	July	5	4.8
11	W. C.	355,327	+	+	○	.....	July	5	4.7
12	E. O.	355,435	+	○	+	Primary of lip	July	5	4.8
13	A. F.	355,549	○	○	+	.....	July	6	4.5
14	C. R.	366,635	+	○	+	.....	August	4	3.6
15	H. L.	355,830	+	○	○	.....	August	4	5.0
16	L. T.	355,956	+	+	+	.....	August	4	4.45
17	J. B.	376,333	+	+	○	.....	August	5	4.4
18	E. R.	368,574	+	○	+	.....	Sept.	4	3.9
19	G. C.	357,027	+	○	○	.....	Sept.	5	4.5
20	R. R.	357,342	+	○	+	.....	Sept.	4½	3.4
21	S. S.	357,509	+	○	+	.....	Sept.	5	4.5
22	H. B.	357,890	○	○	+	.....	Sept.	5½	4.2
23	B. S.	357,740	+	○	+	Primary of lip	October	6	4.0
24	J. K.	358,034	+	○	+	.....	October	6	2.8
25	T. H.	358,321	+	○	○	.....	October	5	4.3

Two patients succeeded in reinfecting themselves with syphilis. In the 1 instance, the evidence is beyond doubt; in the other, highly presumptive. The first of these (Case 3) was admitted to our Service in June, 1933, with primary and secondary lesions. The dark field was positive. His Wassermann was 4+. Over the course of 4 days he received 3.5 gm. of neoarsphenamine. At the end of the second month of observation his Wassermann was ±; at the end of the 3rd, 4th, 8th, and 18th months, negative. He returned 38 months after the first infection and 18 months after the last negative Wassermann, with a sore on his penis that had been present for 3 days. He admitted frequent exposure. The primary infection in 1933 had been at the urethral meatus. The new lesion was in the coronal sulcus near the base, and was quite indurated. Firm, enlarged lymph nodes were present in the groin. The dark-field examination from the new sore showed many typical Spirocheta pallida. His

CHART 2.—WASSERMANN REACTION.

Case number.	Adm.	Blood (Months).																			Spinal fluid.	Date.	Teleoroentgenogram.	
		1	2	3	4	5	6	7	8	9	10	11	12	18	24	30	36	42	48	54	60			Date.	Result.
1	4+	4+	1+	○	..	..	..	..	..	..	..	..	..	○	..	..	..	..	..	○	See text				
2	4+	4+	4+	4+	3+	..	..	..	..	..	..	..	○	○	..	..	..	..	..	○	..	○	Mar., 1938	Mar., 1938	Normal.
3	4+	4+	±	○	○	..	..	..	○	..	..	..	..	○	..	Re-infection			See text		..	○	Dec., 1934		
4	4+	4+	○	○	○	..	..	..	..	..	..	..	..	..	..	..	..	○	..	..	..	○	Mar., 1938	Mar., 1938	Normal.
5	4+	4+	4+	Lost																		See text			
6	3+	3+	4+	4+	4+	Lost																			
7	4+	3+	○	○	○	..	..	○	..	..	○	..	○	○	○	○	○	○	○	○	..	○	Nov., 1934		
8	4+	4+	○	○	..	..	..	○	..	○	..	..	○	○	Re-infection (?)				See text		..	○	July, 1934		
9	4+	4+	○	Lost																					
10	4+	Lost																							
11	○	2+	○	○	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	○	..	○	Apr., 1938	Mar., 1938	Normal.
12	4+	4+	2+	○	..	..	..	..	○																
13	4+	Lost																							
14	4+	4+	4+	○	..	..	○	..	..	..	..	..	○	○	○	○	○	○	○	○	..	○	May, 1934	Mar., 1938	Normal.
15	4+	4+	4+	4+	4+	4+	4+	4+	4+	4+	4+	4+	○												
16	4+	○	○	Lost																					
17	1+	±	○	○	..	..	..	..	..	..	○	..	○	○	○	○	..	..	..	..	..	○	Feb , 1935		
18	4+	4+	3+	○	..	..	..	○	○	..	..	..	..	○	○	○	○	○	○	○	..	○	July, 1934	Nov., 1937	Normal.
19	4+	4+	○	○	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	○	..	○	Mar., 1938	Mar., 1938	Normal.
20	4+	4+	..	..	..	..	..	..	○	..	..	..	..	..	..	..	..	..	..	○	..	○	Mar., 1938	Mar., 1938	Normal.
21	4+	4+	○	○	○	Lost																			
22	4+	..	..	..	..	..	..	..	..	..	..	..	..	..	See text										
23	4+	4+	○	○	..	..	..	..	..	..	○	..	..	..	..	○									
24	4+	4+	Lost																						
25	4+	4+	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	○	..	○	Mar., 1938	Mar., 1938	Normal.

blood Wassermann was still negative. Treatment was deliberately withheld, and 3 days later the dark-field examination was still positive. Two days later a macular lesion appeared on the trunk, the left epitrochlear gland became enlarged, the primary sore was now chancroidal, and smears showed the Ducrey bacillus. Nineteen days after the first appearance of the patient, the macular eruption was still visible and the blood Wassermann test was 4+. Treatment was deliberately withheld until all of the data of reinfection could be obtained. He was now given bismuth intramuscularly and arsphenamine intravenously. He has been under treatment to date for 18 months by the conventional methods. His Wassermann is still positive, as contrasted to Wassermann negativity obtained in 3 months by the massive dose therapy. During the course of the second treatment there were no unusual toxic or allergic reactions, demonstrating that the patient had not been sensitized to arsenic by the massive dosage.

In the other patient (Case 8), the evidence that reinfection also occurred is presumptive, but not completely proven. He was first admitted with secondary syphilis and a 4+ Wassermann. Originally, he was given 4.6 gm. of neoarsphenamine over the course of 5 days. At the end of 2 months his Wassermann was negative and he had negative Wassermanns at the 3d, 7th, 9th, 12th, and 19th months of observation. His last Wassermann was performed on February 14, 1935, at which time he was clinically well. This patient was a profound alcoholic and indulged in frequent and promiscuous sexual relationship. One week prior to his last Wassermann he had had repeated sexual exposure, and 3 genital sores appeared immediately after his last visit, or 1 week following the last sexual exposure. One of the sores was at the site of the previous lesion, one was in the sulcus, and the third was on the glans penis. He had been treating the lesions himself with carbolic ointment and aristol powder for the 4 weeks that ensued between the visits. Two dark-field examinations were negative. Blood Wassermann test was 4+. The lesions assumed a chancroidal character and showed a tendency to heal; a month later they were virtually healed. There was no eruption. The right inguinal nodes were aspirated, but no Spirocheta pallida could be demonstrated. The coronal ulcer was aspirated and this was similarly negative. Treatment had been deliberately withheld. However, the patient went to a private physician who immediately instituted therapy. The critical reader may form his own conclusion as to whether this was a recrudescence of the original infection, a superinfection, or a reinfection.

Comment. It would be hazardous and unsafe to draw conclusions or calculate percentages on a series of cases so small and on observations that are so imperfect. One claim, however, seems completely justified. This would hold that primary and early secondary

syphilis may not only be "cured" by the massive injection of neoarsphenamine, by the method we have described, but that a permanent and complete result is possible though no other therapy is introduced in any way or at any time.

If primary and early secondary syphilis can be cured and remain cured as the result of 4 or 5 days of intensive treatment, a means for the successful eradication of this dread disease is at hand. The possibilities present a new vision of the syphilis problem for public health officials and legislators. If the further work corroborates our findings that the method is free from excessive hazards, beyond the expectancy in any of the usual forms of arsenotherapy and that, under scrupulously controlled technique, the method may be applied to the routine treatment of syphilis, the significance of these observations to the patient as an individual and to the community as a whole, both in the public health aspects and in the economics of chronic disease, can scarcely be overstated or overemphasized. At the present time, however, the method must be considered experimental and should not be practiced in the routine treatment of syphilis until there has accumulated a much greater experience than we have reported. Should our experiences and findings be confirmed, there will have been accomplished the chemotherapeutic goal that Ehrlich sought—"sterilisatio magna."

The original work on this problem was made possible through the generosity of the late Ernst Rosenfeld.

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FOUR PHYSIOTHERAPEUTIC DEVICES FOR THE TREATMENT OF PERIPHERAL VASCULAR DISORDERS.

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The purpose of this presentation is to describe four physiotherapeutic devices for the treatment of peripheral vascular disease. They have been used successfully at this hospital for periods of from 1 to 4 years.

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Three of these devices were constructed by one of us (H. M.) to carry out forms of therapy already well known, namely, controlled heating, alternate suction and pressure, and iontophoresis. The advantage over apparatus previously described lies solely in their simplicity, portability, and small expense. These factors have permitted us to construct many units, to treat a much larger number of patients, and to shorten the duration of hospitalization by supplying apparatus for patients to take home with them.

The fourth device (designed by I. S.), is a bed altered to permit the patient to rest with his legs dependent. Its purpose is to increase the hydrostatic factor of the blood pressure in the leg arteries, and so to improve the circulation through partly occluded vessels. A thermo-regulated cradle is built into it. This bed has proved especially useful in treating patients with rest pain so great that the horizontal position of the leg could not be tolerated.

Besides the details of construction, a brief review of the literature and directions for using the apparatus will be given.

A Simple Thermoregulator for Maintaining Optimum Temperature in a Foot Cradle. Starr[15] and Severinghaus[14] have described thermoregulated cradles, and these devices have been used for a sufficient time to prove that they will relieve pain in many cases of peripheral vascular disease. A number of types are on the market. The cheapest of which we have knowledge sells for $50.

A simplified form of such apparatus is shown in Figure 1. The letters show the parts mentioned in the text. To construct it one needs:

1. One 60-watt electric light bulb (A, Fig. 1).
2. One electric light socket and switch, cord, and plug for connection with house current.
3. A simple adjustable thermostat with thermometer* (B, Fig. 1).
4. A piece of $\frac{1}{32}$ inch hard black vulcanized fiber sheet, 12 by 16 inches.†
5. One piece of copper sheeting, $\frac{1}{32}$ inch thick, 1 inch by 6 inches.
6. Board for mounting approximately 17 inches by $3\frac{1}{2}$ inches, by $\frac{1}{4}$ inch. The total cost of materials is approximately $10.

This apparatus is mounted on the board, the copper sheet being bent to support the light socket. Two layers of fiber sheet are bent around the light bulb, as shown. The inner layer must be at least $\frac{1}{2}$ inch from the bulb at the nearest point. The outer layer is fastened upon the inner layer at the mounting board, but extends 1

* We use a device manufactured for regulating the heat of houses; a United Electric Controls Company (69 A St., Boston) No. 11 Thermostat. For a slight additional cost the manufacturer has altered the range to meet our requirements, 80° to 105° F. We have obtained this thermostat, so altered, from the Pennsylvania Distributing Company, 2401 Chestnut St., Philadelphia, Pa., at a cost of about $8.50. The order should specify "without outlet box" as the latter, usually sold with the thermoregulator, is not needed.

† Obtainable from the Wilmington Fibre Specialty Company, Wilmington, Del.

inch beyond the inner layer at the greatest distance from the mounting board. Anyone assembling this apparatus must absolutely assure himself that the patient's foot cannot come in contact with either the bulb or the inner layer of the guard.

This apparatus is hung inside any leg cradle with the lamp end up. The thermostat is adjusted, usually by the patient himself, until a maximum of comfort is obtained. In our experience, the temperature selected is usually between 85 and 95° F. The feet of hospital patients are maintained at this temperature constantly whenever they are in bed. If they must leave the hospital before pain is gone or lesions completely healed, they take a thermoregulator home with them and use it until all acute symptoms have subsided.

These thermoregulators have also been employed in the treatment of certain patients with reduced circulation to the feet but without either rest, pain or acute lesions. A number of intelligent elderly arteriosclerotic patients, who complained chiefly of cold feet, have received great comfort by using a thermoregulated cradle at night during the winter months. As the incidence of acute lesions in peripheral vascular disease is much greater in winter than in summer, one has the right to expect that maintaining the temperature of the feet in such cases may prevent the development of lesions. It is hoped that the greater availability due to lessened expense may make possible a more exact study of this subject.

Simple Apparatus for the Application of Alternate Suction and Pressure to the Fingers. Alternate suction and pressure for the treatment of peripheral vascular disease has been studied and advocated by Landis and Gibbon,[8a,b] by Reid and Herrmann,[12] and by Herrmann and Reid.[5] Occasionally the digital arteries are mainly involved, and the outstanding complaint is of an indolent lesion localized to a digit. Symptomatic relief can often be obtained by frequent application of suction and pressure to this most affected part. The simple apparatus to be described was designed to apply alternate suction and pressure to any finger. It can be used by the patient at home. The necessary materials cost less than $1.00.

One needs (1) a section of glass tubing to fit the fingers loosely (Fig. 2). We use a piece 5 inches long, of 1 inch internal diameter, $\frac{1}{16}$ inch wall, with flamed ends; (2) surgical drainage tubing 1 or $1\frac{1}{4}$ inches across when lying flat; (3) one No. 6 rubber stopper with hole bored to fit a (4) glass or metal connecting-tube running to (5) a rubber bulb with single opening and without valves ("blind bulb," $1\frac{1}{2}$ inches by $2\frac{5}{8}$ inches). This bulb should be chosen with some care as it must given negative pressure of 100 mm. Hg. All bulbs should be tested with a mercury manometer before buying or using them for this purpose.

The apparatus is assembled as shown in Figure 3. The drainage tube is employed as a cuff to make an air-tight joint between finger

and glass tube. Lanolin is used to make the joint between cuff and finger air tight. Tight constriction of the finger by the rubber is to be avoided and it is unnecessary. The bulb is attached when it is partly compressed. Suction is applied to the finger by allowing the bulb to expand, and pressure is applied by compressing the bulb with the fingers of the other hand.

Four patients with advanced thrombo-angiitis obliterans of the fingers have been treated, the patients taking the apparatus home with them, and giving the treatment themselves. Treatment consisted of suction for 10 seconds, then of pressure for a sufficient length of time to make the finger blanch. The patients were directed to use the apparatus for a half hour twice daily. In each instance, after 2 weeks to 3 months of treatment, a cold, blue, painful finger became warmer, its color improved, and pain disappeared. No proof of the value of this therapy can be claimed from so short a series of patients, but the principle of the method is similar to that of the accepted methods of Landis and Gibbon[4a,b] and of Herrmann and Reid,[5] for which considerable favorable evidence has accumulated.

No attempt has been made to apply this simple technique to the treatment of toes with occlusive arterial disease but there seems no doubt that it could be used in selected cases. The bulb could be connected by rubber pressure tubing which is long enough to permit the bulb to be held in the hand. If the circulation at the base of the toe is dangerously decreased by disease great care should be taken to avoid chafing from glass or rubber.

deTakats[3] in a recent article implied close similarity between suction and pressure therapy and therapy by intermittent venous occlusion (Collens and Wilensky[2a,b]), the criterion being similarity of color change. By means of the simple suction and pressure apparatus described above, one can illustrate very clearly the color changes in the fingers characteristic of suction and pressure. To study the effects of intermittent venous occlusion under comparable conditions a small inflatable cuff of thin rubber and silk was constructed for application to the base of the fingers. This cuff was rhythmically inflated with the pressures and timing advocated by Collens and Wilensky for the leg.

In normal fingers the suction phase of our apparatus produced reddening of the skin within a second while the pressure phase produced immediate blanching. In contrast to this intermittent venous occlusion caused a slow increase in skin color, and the skin became slightly cyanotic. Release of occlusion permitted slow return of normal color. In other words, the changes of color seen under suction and pressure are more rapid and intense than those produced by intermittent venous occlusion.

An Apparatus for Giving Drugs by Iontophoresis. Treatment by iontophoresis had a vogue about 40 years ago but it was soon largely

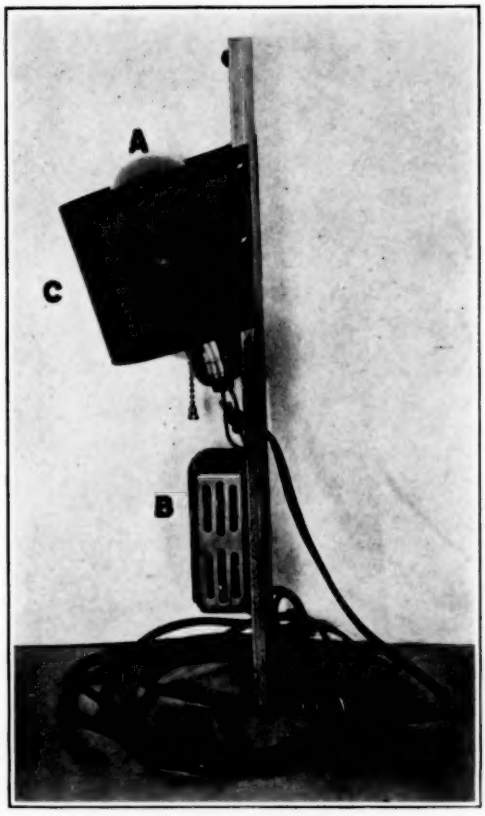

FIG. 1.—A simple thermoregulator for maintaining optimum temperature in a foot cradle. *A*, 60-watt bulb; *B*, thermostat; *C*, lamp guard.

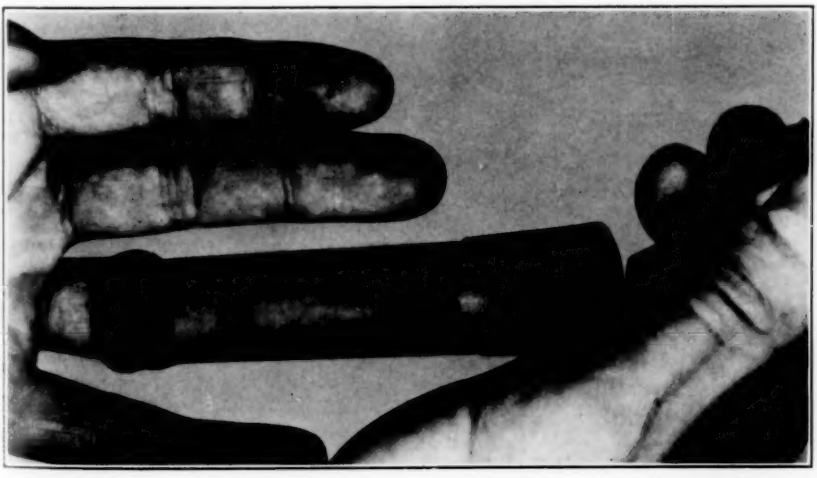

FIG. 2.—A simple apparatus for application of alternate suction and pressure to the fingers.

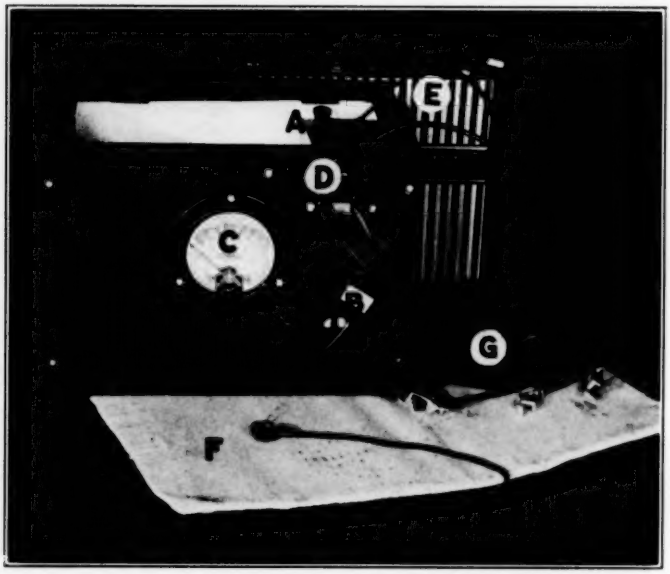

FIG. 3.—Apparatus for iontophoresis. *A*, portable battery; *B*, variable resistance; *C*, milliammeter; *D*, tip jacks; *E*, long-life battery; *F*, negative electrode; *G*, lead wires; *H*, alligator clips; *I*, terminal of negative electrode.

FIG. 4.—A bed altered to permit a dependent position of the legs (see text).

abandoned. Kovacs[6] reopened the subject by introducing mecholyl iontophoresis for the treatment of arthritis. But the interest soon turned to its use in peripheral vascular disease.[6,7,10,13] The necessary apparatus can be obtained from various manufacturers at a cost which has varied from $125 to $15. We have been using apparatus the parts of which can be bought at any radio supply store and assembled for about $15.00. Ten of these outfits are now in use and have been entirely satisfactory.

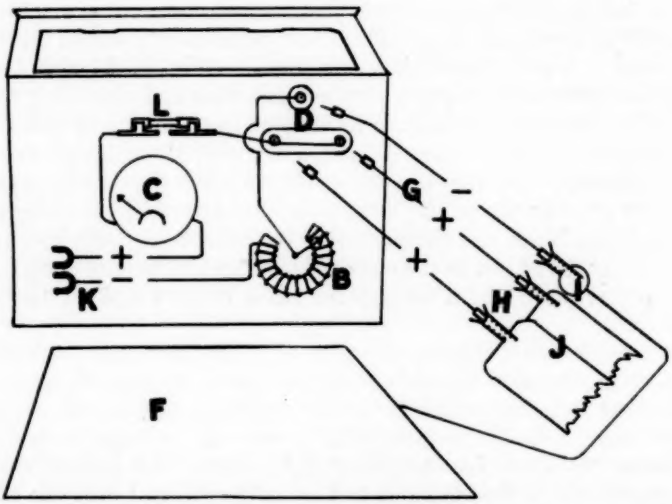

FIG. 3 A.—Apparatus for iontophoresis—Wiring Diagram. Designations by letter correspond to those in Fig. 3. *J*, metal sheeting of positive electrodes; *K*, spade lugs; *L*, fuse.

The parts are (1) a steel cabinet, 10 by 7 by 6 inches (Bud No. 993); (2) one 50 MA. milliammeter (Triplett No. 321); (3) one 10,000 ohm variable resistance (Yaxley E-10M-P) with knob; (4) one fuse-holder and three $\frac{1}{16}$ ampere fuses (two are spares); (5) one 45V "B" battery (Burgess No. 5308) for use in the portable cabinet; or No. 21308, a larger battery, with a longer life, and so more satisfactory for use in the clinic. These batteries have three terminals labelled: "−", "+22.5", and "+45"; 22.5 volts can be drawn by using the terminal marked 22.5 and either of the other terminals. (6) One red single insulated tip jack (negative pole) and (7) one black twin insulated tip jack (positive pole); (8) 10 feet of red and 20 feet of black rubber-covered braided wire (Kinkless RC) for lead wires (to electrodes on patient); (9) one red and two black tip plugs for attaching one end of lead wires to tip jacks; (10) one red and two black insulated alligator clips for attaching the other end of the lead wires to the electrodes (2 positive, 1 negative), and (11) two

insulated spade lugs (one red, one black) for attaching two short wires (2 feet long) to the battery.

The apparatus is assembled as follows (Figs. 3 and 3A): The front panel of the cabinet is removed by taking out the screws shown at the four corners, and holes are cut to take the shaft of the variable resistance (B), the milliammeter (C), and the tip jacks (D). The fuse holder is fastened by a screw which shows 1 inch to the left of (D). A series circuit from the red (negative-upper) tip jack through the resistance, the battery, the ammeter, the fuse, and back to the black (positive-lower) tip jack is made by means of soldering lengths of insulated wire. The front panel of the cabinet is then replaced. A red wire with spade lug (K—Fig. 3, A) goes to the negative pole of the battery and a black wire and spade lug to the positive, marked 22.5 V. An 8-foot red (negative) and two 8-foot black (positive) lead wires (G) are used, with tip plugs on one end and alligator clips (H) on the other. Either the small, portable battery (A, Fig. 3), or the large long-life battery (E) may be used. A combined brace and compartment (not shown) is made by cutting a piece of wood to fit in the left end panel and attaching it vertically to another piece which wedges the small battery against the right end panel.*

A negative (indifferent) electrode (F., Fig. 3 or 3A), for application to the back of the thorax, is illustrated because we have seen none that seems as satisfactory. It consists of copper wire screening with edges heavily covered with sewed cotton tape, covered by oversize (to allow for shrinking) light duck. An end of rubber-insulated wire is braided and tied by cotton thread into one end of the copper screening. This electrode makes excellent contact, has long life, and we have seen no more than a mild erythema result when 10 to 35 milliamperes of current have been used. It cannot be bought, but can easily be made. Descriptions of satisfactory positive electrodes used to make contact between drug solution and the limb under treatment, can be found in papers by Kovacs,[6] Kramer,[7] and Cohn and Benson.[1] A common form consists of a 15 inch by 2½ inch piece of diathermy metal sheeting ("medium electrode foil" (obtainable from any Roentgen ray supply store), reinforced asbestos paper (Merck & Co.), and a 3 inch Ace Bandage.

Our experience in the use of iontophoresis is confined to the treatment with Mecholyl. The method to be described differs in no essential way from that used by others.[6,7] The spade lugs are attached to the battery terminals. The lead wires (G) are attached by plugging into the tip jacks (D). All the resistance is thrown into the circuit by turning knob B counter-clockwise as far as it will go. A couch is covered with rubber sheeting and turkish towels.

* The Radio Department of the M. and H. Sporting Goods Store, 512 Market Street, Philadelphia, Pa., supplied these parts and assembled them for us at a total cost of $15.40.

The negative electrode is prepared by soaking it and a hand towel in warm tap water. A small mat of rubber is laid on the turkish toweling which covers the couch, the electrode is placed on this and the wet hand towel is placed on the electrode. The patient, wearing only a hospital gown with an open back, reclines on the couch with the wet towel in contact with his back.

Either one or two positive electrodes can be used. The asbestos paper and the Ace bandage are soaked in a 0.2% solution of Mecholyl. The part to be treated is surrounded by one layer of wet asbestos paper. Two more layers, each a little larger than the metal sheeting, are laid on the first layer, and the metal sheet is laid on this triple thickness of paper. The bandage is firmly applied around all of the asbestos paper and all except one end of the metal sheet (J, Fig. 3-A), this end left free and the black lead wire clipped to it.

As an extra precaution against a short circuit, just before passing the current through the patient, the clip (H) of the red (negative) lead wire is made to touch momentarily the clip of a black (positive) lead wire, and the resulting deflection of the ammeter noted. If this is not more than 3 milliamperes the treatment is begun.

When the knob B turned counter-clockwise as far as possible, the clip of the red lead wire is attached to the terminal (I) on the negative electrode. In this way the circuit through the patient is completed. The current is increased slowly by turning the knob (B) clockwise, while the operator watches the needle of the milliammeter. Several minutes should be used in raising the current to the desired level. A strong prickling sensation at the positive or negative electrode indicates that tolerance has been reached, but this sensation becomes less and then more current can be tried. There should be no discomfort during treatment, and from 15 to 25 milliamperes can be used with safety in most cases. The chief danger lies in the burn which will result if the metal of the positive electrode slips off the underlying paper and gets into direct contact with the skin. The patients must be instructed to report any discomfort immediately.

Iontophoresis is usually given three times weekly for periods of one-half hour each time.

Mecholyl iontophoresis has been advocated in the treatment of varicose ulcers,[13] chronic thrombophlebitis,[10] scleroderma,[4] and to some extent in the treatment of limbs with obliterative and spastic arterial disease.[7] The first author's experience with treatment by mecholyl iontophoresis has been restricted to the treatment of 20 patients for periods ranging from 1 week to 1 year.* Of 8 patients with varicose ulcers 1 was unimproved, 3 were healed, and 4 much im-

* Thanks are expressed to Miss Sarah Turner for technical assistance in the treatments with mecholyl iontophoresis, and to Merck & Co., Rahway, N. J., for donating the mecholyl and the reinforced asbestos paper.

proved after treatment for periods varying from 1 week to 4 months. Of 8 patients with chronic thrombophlebitis, 7 were symptomatically relieved in from 1 week to 4 months. Of 4 patients with scleroderma 3 were definitely benefited in from 2 weeks to 8 months.

Only a few untoward effects were encountered. In an asthmatic patient with a varicose ulcer mecholyl iontophoresis (8 milliamperes of current) produced an asthmatic attack. In 1 patient with severe chronic thrombophlebitis and varicose veins, two treatments were followed by chills and fever. It is reasonable to suppose that bacteria or toxic materials were washed from diseased vessels into the general blood stream. It has been shown that the blood flow through a limb is greatly increased by mecholyl iontophoresis.[9]

A Bed Altered to Permit a Dependent Position of the Legs. Before the development of the device to be described some patients with peripheral vascular disease always insisted on hanging their diseased legs out the side of the bed, claiming that any other position was more painful. In several of these cases the reaction of the skin to histamine gave evidence that the circulation was better when the limb was dependent. This was in accord with theoretical expectations as the hydrostatic element in the blood pressure of the peripheral arteries must be increased when the limb is dependent. Pearse and Morton[11] have demonstrated this increased arterial pressure in the arteries of dependent legs of normal persons. The bed pictured in Figure 4 was designed to take advantage of this fact in the treatment of selected cases of peripheral vascular disease. It was constructed at the shop of the Johnson Foundation of the University of Pennsylvania under the direction of Mr. A. J. Rawson.

The spring of an old hospital bed was shortened to a point (A) 30 inches from the foot of the bed. A box fitting inside the spring frame was mounted on a hinged pedestal (B) so that it could be raised and lowered by cords (C) which were tied to the foot to support the free end at the desired height. The lower end of the mattress rested on the floor of the box.

The box was made by nailing a type of wall board, sold under the name of "Masonite," to a wooden frame. It contained two lights, shielded with Masonite guards, placed, one on each side, under the letter D. These were controlled by a DeKhotinsky Thermoregulator (Central Scientific Co.), the outer end of which is shown at the apex of the box (E). A switch is beside it. The total cost of the materials and labor necessary to alter the bed was about $50.

When in use a blanket was placed over the box, so that one edge acted as a curtain to close the aperture through which the feet were inserted. The bed clothing was then thrown over the top of this blanket.

The bed has found its greatest usefulness in the treatment of patients whose pain is relieved by the dependent position. We allow such persons to choose the angle they find most comfortable. Most

of them have preferred to have their feet about 30 degrees below the horizontal when the back rest is down, 45 degrees or more when the back rest is elevated. The relief afforded is often quite striking.

Certain patients with peripheral vascular disease complicated by infected lesions, or by edema, have increased pain when the diseased leg is dependent. These patients are never treated with the legs in the dependent position. The legs may be held level, or elevated by raising the free end of the box.

Summary. Four types of apparatus used in the treatment of peripheral vascular disease at the Hospital of the University of Pennsylvania are described. Three of them are adaptations of devices previously described by other authors, and they are recommended only because they are simpler, more portable, and less expensive than the originals. We describe:

1. A simple thermoregulator, for use in foot cradles.
2. Simple inexpensive apparatus to permit the application of alternate suction and pressure to single digits.
3. Inexpensive apparatus for iontophoresis, constructed from standard radio parts.
4. A bed so altered that the legs can be within a thermoregulated cradle and at the same time be dependent, level or elevated.

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THE DIAGNOSIS OF TULAREMIA.

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During the past 2 years, a study of the cases of tularemia at this hospital indicated the need of rapid, yet reliable methods of diagnosis early in the course of the infection. This is particularly

true because the early administration of specific anti-tularense serum is advocated for therapy.[2d,i,j] An accurate diagnosis is necessary soon after the onset of the tularemic infection, if serum is to be given early.

A definite diagnosis of tularemia is dependent on laboratory procedures. The majority of the ulcero-glandular cases present a rather typical syndrome of contact history (rabbits, ticks), ulcer, marked adenitis, acute illness from 1 to 3 weeks and prolonged convalescence. Although the diagnosis usually can be suspected in these cases, confusion may arise with other infections producing a local ulcer with regional lymphangitis and adenitis. The other types of tularemia, particularly the typhoidal, glandular, and pulmonic forms, often do not present a characteristic clinical picture and are frequently mistaken for other disease entities which they may simulate. The most that the clinician can do in these cases is to suspect the possibility of a tularemic infection.

It is therefore apparent that laboratory procedures are necessary to confirm or establish the diagnosis of tularemia. A positive diagnosis of tularemia cannot be made without the use of one or more of the following diagnostic tests:

1. Blood agglutination.
2. Opsonocytophagic reaction.
3. Skin tests.
   (*a*) Antigen skin test.
   (*b*) Antiserum skin test.
4. Culture of organisms.

It is our purpose to present experience with these diagnostic tests in 50 cases of tularemia. We were particularly interested in the intracutaneous tests[2b,c,g,h] as reported by Foshay, who considers these tests as reliable and diagnostic early in the course of the disease. We attempted to evaluate the various tularemia skin tests in correlation with the other diagnostic procedures commonly used in tularemia. The results of these tests are shown in Table 1. Some of the patients received all of the available tests, while in others it was possible to do only some of them.

Blood Agglutination. The test used in this work did not differ in essentials from that described by Francis and Evans.[5] The antigen used was prepared by growing several strains of *Past. tularensis* (old stock cultures and a recently isolated strain) upon a nutrose-glucose-serum agar containing cystine.[2e] The washed bacteria were killed by 0.4% formalin in 0.85% saline and suspended in saline to give a turbidity equivalent to 100 p.p.m. of kaolin in saline.

Apparently all cases of tularemia develop a positive agglutination—usually during the second week—which persists for the remainder of the life of the patient. All of our 50 cases had positive agglutinations. Those patients whom we saw soon enough for

early observations developed agglutinins during the second week and these gradually increased to a high titer. A titer of at least 1:80 is usually necessary for diagnosis, but lower values may be significant if there has been a previous negative agglutination or if there is a positive skin test and opsonocytophagic reaction. The agglutinin titer may be low several years after recovery from the initial infection (Cases 42 and 45). Cross-agglutination with *Br. abortus* and *B. proteus* OX_{19} may cause some difficulty. Nonspecific agglutination is usually present in a lower dilution and is slower in developing in the water bath. Differentiation is frequently possible by use of the opsonocytophagic reaction and the skin tests.

Opsonocytophagic Reaction. The phagocytic test was essentially the opsonocytophagic test described by Huddleson.[8] The patient's blood (5 cc.) was added to 0.2 cc. of 20% sodium citrate. In some instances, when repeated tests were to be made on the same patient, 1 cc. of blood was added to 0.2 cc. of a 4% sodium citrate solution in saline, using a tuberculin syringe. The test was performed according to the procedure of Evans[1] and a phagocytic index number (P.I.N.) was obtained from the stained slide, using the nomogram of Foshay and LeBlanc.[3] The antigen for this test was prepared by growing the organism on the nutrose-serum-cystine agar described by Foshay,[2c] washing the growth with saline containing 0.4% formalin, and finally suspending in sufficient formalized (0.4%) saline to give a turbidity equivalent to 5000 p.p.m. of kaolin. Before use in the phagocytic test, a portion of this stock suspension was diluted ten times with sterile saline, centrifuged at 3000 R.P.M., and the supernatant fluid was replaced with an equal volume of sterile saline solution. In some instances, it was not possible to obtain the patient's citrated blood before the polymorphonuclear cells had disintegrated. In these cases, serum or plasma from these patients was mixed with equal volumes of the *Past. tularensis* suspension (500 p.p.m. kaolin), and citrated blood from a normal individual (rabbit blood served in some instances). Comparative tests, using this modification and the test as used by Foshay, showed no significant difference between the phagocytic index numbers obtained. The use of serum or plasma* (mixed with fresh citrated blood from a normal individual) for phagocytic tests may prove to be of value to health department laboratories receiving many specimens by mail too late for performance of the opsonocytophagic test as described by Huddleson.[8]

This test becomes positive about the same time as the blood agglutination. The reaction is usually strong after the third or fourth week of the disease and apparently persists as long as the agglutination (Cases 42 and 45). Interpretation of the phagocytic reaction has been quite difficult in some cases. We have observed many weak or even an occasionally strong phagocytosis in a number

* This method is to be published.

of conditions other than tularemia, so that a positive opsonocytophagic reaction in itself is not diagnostic.

The phagocytic reaction serves as an aid to the blood agglutination and skin test, particularly in those cases which have a questionable clinical diagnosis. The test is of value when there is a cross-agglutination between *Past. tularensis* and the Brucella group. Foshay[2a] states that he has never observed an instance of cross-phagocytosis in patients who cross-agglutinated with either Brucella organisms or *Past. tularensis*. He considers this a most useful test for verifying the coexistence of these two diseases or for excluding one from the other.

The phagocytic reaction was usually strong after 2 or 3 weeks in the course of the illness, regardless of the clinical condition of the patient. However, in a few cases the reaction was weak in patients who were not reacting favorably to the infection.

Skin Tests. There are two main types of tularemic skin tests as described by Foshay—the antigen[2c,g] and antiserum.[2b,h] According to Foshay, these skin tests are diagnostic for tularemia from the first day of illness to at least the twenty-second year after complete recovery, or apparently the remainder of the life of the patient.

Antigen Skin Test. An intracutaneous injection of a suspension of detoxified *Past. tularensis* organisms (treated by formalin and nitrous acid[2f] according to Foshay) was used for this test. The suspension was equivalent to 50 p.p.m. of kaolin and 0.05 cc. was injected intracutaneously. This antigen was used also for treatment of chronic cases and for immunization of animals for the production of diagnostic and therapeutic antisera. In our work, a suspension of Brucella organisms was used simultaneously as a control skin test.

A positive test is a delayed tuberculin-type of reaction, consisting of erythema and induration. It is read in 48 hours. The reaction is usually quite marked with local tenderness, without constitutional reaction, and tends to persist for from a few days to several weeks. This type of skin test appears to be specific and diagnostic early in the disease. The test was used in 32 proven cases of tularemia and was positive in all. In our experience, the test was positive in the first week of the disease (Cases 3, 12, 21, 23, 26, 30 and 36) and reacted positively several years after the onset of the infection (Cases 41, 44 and 48). A few normal individuals developed a slight nonspecific reaction which resembled the weakly positive reaction observed in some tularemic patients early in the infection. A nonspecific reaction usually faded rapidly after 36 to 48 hours, while a specific reaction generally persisted for a week or longer. A doubtful reaction should be repeated with the same antigen or a more concentrated suspension. It is important that the individual who observes the skin test reaction in the patient be familiar with the doubtful or non-specific reactions which a given antigen may produce in normal individuals. The usual case of tularemia will show

an unquestionable reaction with marked induration and erythema. In colored patients, this test was of definite value (Cases 46 and 47), whereas the antiserum skin test could not be read in deeply pigmented skins. The antigen skin test was positive even when the horse and goat antiserum skin tests were negative (Cases 35, 36 and 37). We have not seen a negative antigen skin test in a patient with a proven tularemic infection. We have checked this skin test in a large number of normal patients and in numerous clinical conditions and have found it to be one of our most reliable tests.

Antiserum Skin Test. The intracutaneous injection of specific tularense antiserum was described by Foshay[2b,h] as a diagnostic test for tularemia, suitable for use early in the course of the disease. The response in patients with tularemia to an intracutaneous injection of a 1 to 10 dilution of the antiserum is the production of erythema and edema at the site of injection, the maximum reaction occurring in 20 to 30 minutes. A control intracutaneous injection of a 1 to 10 dilution of normal serum should show no erythema or edema. It is essential in this test that a suitable control serum be used, but as emphasized by Foshay[2h] it is necessary to use great care in the selection of animals for normal serum as well as for the production of reliable diagnostic antiserum if one wishes to avoid non-specific reactions in the diagnostic test. We have used commercial (Mulford-therapeutic) antitularense horse serum,* antitularense goat serum (received from Foshay), and human convalescent serum obtained from some of our tularemia patients.

In our experience, if the antiserum test showed a definite positive reaction and the control serum was negative, a diagnosis of tularemia could be made and was always substantiated later by the blood agglutination and the antigen skin test. If the control serum showed even a mild reaction the test was of no value, regardless of how intense the specific antiserum reaction might be. Of the positive control reactions, many did not show a typical allergic response, with urticarial wheals, itching, and so on, and the conjunctival test for sensitivity to the control serum was usually negative. The response to an intracutaneous injection of this control serum was an erythematous-edematous reaction.

The antitularense horse serum (Mulford-therapeutic) skin test was employed in 35 cases of proven tularemia (Table 1). This test was diagnostic in 12 cases, but in 20 the patients exhibited positive control reactions. Three cases showed no reaction to either serum or to the control test. The test was therefore of value in only about one-third of our patients. The test was diagnostic early in the disease before the blood agglutination was positive (Cases 1, 3, 4, 6, 9 and 12) and later (Cases 2, 5, 10 and 11). Antitularense goat serum (received from Foshay) was used on 21 proven cases of tularemia.

* This product was supplied to us through the kindness of Dr. W. A. Feirer of Sharp & Dohme (Mulford Biological Laboratories).

TABLE 1.—RESULTS OF DIAGNOSTIC TESTS IN TULAREMIA PATIENTS.*

Case No.	Day of disease.	Blood agglutination titer.	Opsonocytophagic reaction.	Skin tests.				
				Horse tularense antiserum.	Horse control serum.	Goat tularense antiserum.	Goat control serum.	Antigen.
1	3	Neg.	....	++++	Neg.			
	7	1:20						
	24	1:320						
2	55	1:320	....	++++	Neg.			
3	6	Neg.	....	++++	Neg.	++	+++	++++
	13	1:160						
	43	1:640	Strong					
4	12	Neg.	....	+++	Neg.			
	20	1:320						
	45	1:5120						
5	21	1:1280	....	+++	Neg.			
6	8	Neg.	....	+++	Neg.			
	11	1:320						
7	7	1:640	....	+++	Neg.			
8	11	1:320	....	+++	Neg.			
9	5	Neg.	....	+++	Neg.			
	17	1:320						
10	20	1:640						
	56	1:320	....	++	Neg.			
11	20	1:320	....	++	Neg.			
12	6	Neg.	Neg.	+	Neg.	+	Neg.	++++
	69	1:800	Strong					
13	7	Neg.	....	++++	+			
	12	1:320						
14	5	Neg.	....	+++	+	++	Neg.	
	10	1:320						
15	15	1:640	....	+++	+			
	28	1:640						
16	42	1:5120	Strong	+++	+	+	++	+++
17	52	1:320	....	+++	+			
18	15	1:640	Strong	++	+	++	++	++++
	34	1:640	Strong					
19	40	1:1280	Strong	++	+	++	++	++++
	80	1:640	Strong					
20	17	1:80	Moderate	++	++	++	++	++++
	44	1:1280	Strong					
	137	1:5120	Strong					
21	7	1:160	Strong	++	++	++	++	++++
	35	1:400	Strong					
22	8	1:160	....	++++	++			
23	7	1:40	....	+++	++	+++	Neg.	++++
	30	1:640						
24	5	Neg.	....	++++	+++			
	18	1:320						
25	17	1:2560	Weak	+++	+++	+	+	++++
	81	1:800	Strong					
26	7	1:40	Weak	+++	+++	++++	Neg.	++++
	67	1:640	Strong					
27	1	Neg.	Neg.					
	10	1:80	Neg.	+++	+++	+++	Neg.	+*
	90	1:800	Strong					
28	12	1:40	....	+++	+++			
	14	1:80						
29	23	1:5120	Strong	++++	++++	++	Neg.	++++
30	7	1:640	....	++++	++++	++++	Neg.	++++
	30	1:3200	Strong					
31	25	1:1280	....	++	+++			
32	21	1:640	Strong	++	++++	+++	Neg.	++++
	26	1:3200						
33	16	1:6400	Strong	...	...	++++	++++	++++
34	16	1:3200	Weak	...	...	++++	++++	++++
35	10	1:40	....	Neg.	Neg.	Neg.	Neg.	++++
	20	1:80	Moderate	Neg.	Neg.	Neg.	Neg.	
	52	1:1600	Strong					
36	4	Neg.	....	Neg.	Neg.	Neg.	Neg.	++++
	13	1:320	Weak	Neg.	Neg.	Neg.	Neg.	
37	130	1:2560	....	Neg.	Neg.	Neg.	Neg.	++++
38	21	1:2560	Strong	...	...	...	...	++++
39	1½ yrs.	1:80	Strong	...	...	...	...	++++
40	1½ yrs.	1:160	Strong	...	...	...	...	++++
41	4 yrs.	1:80	Weak	...	...	...	...	++++
42	1½ yrs.	1:320	Strong	...	...	+	++	+
43	330	1:800	Strong	...	...	...	...	++++
44	6 yrs.	1:40	Moderate	...	...	...	...	++++
45	6 mos.	1:640	V. strong	...	...	...	...	+++
46†	40	1:320	....	±	±	±	±	++++
47‡	90	1:2560	Strong	±	±	±	±	++++
48	4 yrs.	1:320	Strong	...	...	...	...	++++
49	35	1:1280	Strong	...	...	...	...	+++
50	30	1:640	Strong	...	...	...	...	++++

* The degree of reaction is graded from + to ++++; the + indicating a mildly positive reaction, the ++++ a markedly positive reaction.

† 1:10 dilution of antigen used in this case.

‡ Colored patients.

It was diagnostic in 8 cases while 10 showed a positive control reaction and 3 gave no reaction to either antiserum or normal control serum. The use of convalescent human serum as a skin test has been entirely unsatisfactory in our hands. Serum was obtained from 3 patients who had completely recovered from a recent tularemic infection. The reactions obtained in normal and tularemic patients were variable and unreliable.

The diagnostic antiserum skin test deserves further study. The value of the test has been demonstrated here frequently, but its usefulness has been limited in our work because we have been unable to find suitable control sera. Among the few animals available for experimental work, we have been unable to find any whose sera did not give edematous-erythematous reactions in many normal individuals. In our experience, the test has been of aid in about one-third of the patients because of non-specific reactions.

Culture of Organisms. Although the culture of *Past. tularensis* from an infected patient affords the most definite diagnosis of tularemia, the method usually requires animal inoculation with consequent hazard to non-immune laboratory workers. The disease is easily transmitted from an infected animal to man, regardless of the precautions taken. Francis[4] states that 41 workers in 13 laboratories in the United States, England, Japan and Russia contracted the disease performing necropsies on infected guinea-pigs and rabbits or from handling infected living ticks. The culture of *Past. tularensis* requires so much time that it is of little value to the clinician interested in specific serum therapy early in the course of the disease. The other methods of diagnosis are so reliable that culture of the organism is rarely necessary.

Previous Infection. The possibility of a previous tularemic infection must be eliminated, since the blood agglutination, opsonocytophagic reaction and the skin tests remain positive for years after recovery from the initial infection. The clinical history, physical findings of an active tularemic infection, a rapidly rising blood agglutinin titer, and culture of *Past. tularensis* from the lesions are the most important means of differentiating a previous tularemic infection from one recently acquired.

Effect of Tularense Antiserum on Diagnostic Tests. A diagnosis of tularemia was made on a number of patients during the first week of the illness on the basis of skin tests, before the blood agglutination was positive. These patients received therapeutic antitularense serum and during the second week of the illness developed positive agglutinations of a high titer. The question arose as to whether or not the serum itself could cause a positive blood agglutination in a non-tularemic patient and that perhaps some of these cases treated on the basis of a positive skin test did not have tularemia.

Three normal individuals were tested for agglutination and phago-

cytosis of *Past. tularensis*. On the following day each received 15 cc. of commercial therapeutic antitularense horse serum, intravenously. Five minutes and 1 hour, as well as 24 hours later, blood specimens, were obtained and tested for agglutination and phagocytic activity. The following day (immediately following removal of the 24-hour blood specimen) an additional 15 cc. of antitularense horse serum was given intravenously. Blood specimens taken 5 minutes, 1 hour and 24 hours later, were tested for phagocytosis and agglutination of *Past. tularensis*. The commercial antiserum employed had an agglutination titer of 1 to 320 against the antigen used in the agglutination tests and induced a very strong phagocytosis of *Past. tularensis* organisms when added to citrated blood from a normal individual. The results of the test are shown in Table 2. Case 1

TABLE 2.—EFFECT OF ANTITULARENSE SERUM (HORSE) ON AGGLUTININ TITER AND OPSONOCYTOPHAGIC REACTION IN NON-TULAREMIC PATIENTS.

			1st injection 15 cc. antiserum intravenously.			2d injection 15 cc. antiserum i.v. (24 hrs. after 1st injection).				
	Case No.	Before antiserum.	5 min. after.	60 min. after.	24 hrs. after.	5 min. after.	60 min. after.	24 hrs. after.	7 days after.	14 days after.
Agglutinin Titer.	1	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.
	2	Neg.	1:20	1:20	1:20	1:20	1:20	1:20	1:10	1:20*
	3	Neg.	Neg.	Neg.	1:5	1:5*	1:5	1:5*	Neg.	Neg.
Opsono-cytophagic reaction.	1	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.
	2	Neg. (P.I.N. 5)	Moderate (P.I.N. 48)	Neg. (P.I.N. 2)	V. Strong (P.I.N. 88)	V. Strong (P.I.N. 86)	V. Strong (P.I.N. 90)	V. Strong (P.I.N. 86)	Neg. (P.I.N. 14)	Neg. (P.I.N. 4)
	3	Neg.	Moderate (P.I.N. 46)	Moderate (P.I.N. 58)	Neg. (P.I.N. 10)	Neg. (P.I.N. 10)	Neg. (P.I.N. 4)	Weak (P.I.N. 20)	Neg.	Neg.

Note: Brucella abortus agglutination and phagocytosis tests were all negative.

showed no agglutination or opsonocytophagic reaction following this serum. Cases 2 and 3 developed very weak agglutination titers which were practically negative after 2 weeks. The opsonocytophagic reaction showed an interesting transitory reaction, particularly in Case 2, but was negative in all 3 cases after 14 days. Although only 3 subjects were used in this experiment, it seems that antitularense serum therapeutically has little or no effect in producing a positive blood agglutination, but may cause a transitory opsonocytophagic reaction.

Effect of Antigen Skin Test on Diagnostic Tests. Goldstein,[6] Heathman,[7] and Evans[1] have shown that intracutaneous tests with heat-killed Brucella suspensions or purified nucleoprotein stimulate the production of agglutinins in a large percentage of subjects. Since the *Past. tularensis* antigen skin test is used early in the course of the disease, before the blood agglutination is positive, it is important to know whether the intracutaneous test itself can stimulate

the production of opsonins and agglutinins. The sera of 12 patients (tuberculous) were tested for phagocytic activity as well as agglutination of a *Past. tularensis* antigen before being given an intracutaneous injection of 0.05 cc. suspension of detoxified *Past. tularensis* organisms (50 p.p.m. kaolin turbidity). Two weeks later specimens of blood were drawn for phagocytic tests and agglutination reactions. A second intracutaneous injection of the detoxified antigen was given at this time. The results of these tests are shown in Table 3. Four of the 12 patients developed positive agglutinations, the highest of which was 1 to 40. An initial agglutination of 1 to 20 in 1 patient was increased to 1 to 40 following the intracutaneous test. Two patients developed weak opsonocytophagic reactions. These

TABLE 3.—EFFECT OF ANTIGEN SKIN TEST ON BLOOD AGGLUTINATION, PHAGOCYTOSIS, AND SUBSEQUENT SKIN TESTS IN NON-TULAREMIC PATIENTS.

	Before vaccine skin test.			14 days after skin test.		
Case No.	Blood agglutination titer.	Opsonocytophagic reaction.	Reaction to initial skin test.	Blood agglutination titer.	Opsonocytophagic reaction.	Reaction to second skin test.
1	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.
2	Neg.	Neg.	Neg.	1:20 ±	Neg.	Neg.
3	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.
4	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.
5	Neg.	Neg.	Neg.	1:40++	Weak (P.I.N. 32)	±
6	Neg.	Neg.	Neg.	1:20 ±	Weak (P.I.N. 25)	±
7	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.
8	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.
9	1:20++	Neg.	Neg.	1:40++	Neg.	Neg.
10	Neg.	Neg.	Neg.	1:20 ±	Neg.	Neg.
11	Neg.	Neg.	±	Neg.	Neg.	Neg.
12	Neg.	Neg.	±	Neg.	Neg.	Neg.

NOTE.—Agglutination reactions and phagocytosis tests of patients' serum for *Br. abortus* were negative throughout.

2 patients also developed mildly positive skin tests. It is apparent then that the effect of the tularense antigen skin test on the blood agglutination and phagocytic reaction is almost negligible.

Conclusions. 1. The results of diagnostic tests in 50 cases of tularemia are presented.

2. The blood agglutination is the most constant and reliable diagnostic method after the first week of the disease.

3. The antigen skin test is positive during the first week of the disease and appears to be highly specific and reliable.

4. The antiserum skin tests, both goat and horse, have been of value in only a small percentage of cases, because of non-specific reactions of control sera. It is always necessary to use a control serum in this test.

5. The opsonocytophagic reaction tends to parallel the blood agglutination in time of appearance and is valuable in differentiating Brucellosis from tularemia, when cross-agglutination occurs.

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SPONTANEOUS INTERSTITIAL EMPHYSEMA OF THE LUNGS.

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In 1937 Louis Hamman[4] described for the first time a group of cases with a syndrome resulting from the *spontaneous* development of interstitial emphysema of the lungs, and it is appropriate that this interesting clinical entity should be designated as "Hamman's Disease."

Mediastinal emphysema resulting from trauma or pulmonary disease was recognized more than a hundred years ago. Laennec[5] described curious grating sounds and bubbling râles during respiration as diagnostic signs of subpleural and interlobar emphysema of the lungs. These signs were later confirmed by Skoda,[9] while Rokitansky[8] described the pathologic anatomy of mediastinal emphysema following ulceration of the trachea, and pulmonary trauma. Other observers reported that the condition was occasionally *secondary* to pertussis, croup, severe crying, the labor of child bearing, bronchial asthma, straining at stool, the induction of artificial pneumothorax, and pneumonia, especially the post-influenzal pneumonia of the 1918 epidemic. Müller[7] in 1888 described certain clinical aspects of mediastinal emphysema, noting the presence of fine bubbling crepitations synchronous with the heart's action, and observing the disappearance of cardiac dullness. Müller pointed out that the diagnosis was greatly facilitated by the appearance of subcutaneous emphysema.

During the World War the term "pericardial knock" was introduced by Smith,[10] who suggested that a curious sound occasionally heard over the precordium in cases of penetrating wounds of the chest was caused by "air in the interstitial connective tissue of the lung."

In 1928 Lister[6] reported a single case which in all likelihood was an instance of spontaneous interstitial emphysema of the lung, but believed that the "pericardial knock" originated from "partial obstruction of the pulmonary artery by tension or distortion caused by displacement of the lung."

Wolferth and Wood[11] observed an instance of "pericardial knock" associated with spontaneous pneumothorax, but the sounds were no longer audible when they examined the patient several days after the onset of the pain. The sounds were said to have been heard by observers across the room 2 days after the pain appeared.

Achard[1] has produced mediastinal emphysema in dogs experimentally by: 1. Injection of air into the mediastinum; 2. Injection of air directly into the lung or the pleural cavity; 3. Subcutaneous injection of air; 4. Partial tracheal obstruction with a tracheotomy tube in place.

An excellent description of the surgical aspects of mediastinal emphysema is presented by Graham, Singer, and Ballon.[3]

Interstitial emphysema of the lungs is caused by the rupture of alveoli or bronchioles and the escape of air into the interstitial tissue of the lungs. If a large amount of air escapes it may travel along the interstitial bands toward the hilum and enter the mediastinum. A second and perhaps commoner pathway for the air to follow is to pass outward directly to the pleura along interstitial bands where it causes the formation of a bleb which may rupture and produce an ordinary pneumothorax. The air may go in both directions, producing both results.

The spontaneous type of interstitial emphysema described by Hamman is characterized by the sudden development of severe pain in the chest without antecedent trauma or unusual effort. The presence of a "peculiar crunching, crackling, bubbling sound heard over the heart with each contraction" is pathognomonic; additional evidence is afforded by the disappearance or decrease in width of the area of cardiac dullness. The presence of subcutaneous crepitation makes the diagnosis obvious and in certain cases pneumothorax is present. Air may be demonstrated in the mediastinum by Roentgen ray.

Since we have been able to find only 1 certain and 1 probable case report besides the 6 cases described by Hamman, and as interstitial emphysema must be exceedingly common and frequently overlooked, we have thought it of interest to describe in some detail one case which we feel was "spontaneous" and an additional case of interstitial emphysema following labor in a patient with rheumatic heart disease, as the physical findings and clinical picture seem to be identical, whether the condition originates "spontaneously," or from sudden increase in intrapulmonary pressure associated with vigorous or violent exercise.

Case Reports. CASE 1.—At 4 o'clock in the afternoon, a 17-year-old girl, apparently in perfect health, while dribbling a basket ball on the floor of her school gymnasium, was seized with a severe pain in the left chest. Because of the pain she returned to her home and went to bed. Shortly afterwards she heard a curious noise in her chest and told her mother that she thought she had pleurisy. When seen at 8 o'clock the patient was quietly reading a book and did not appear to be acutely ill. She stated that the pain increased when she lay on the left side, and that the noises in her chest "come and go." The pulse was 80, respirations were 18, temperature 98.4°, blood pressure 130/80. The only finding of interest on physical examination was the presence of distant soft crepitant sounds, localized to the precordium and of maximal intensity beneath the middle third of the sternum. There was definite association of these sounds with the cardiac contractions, but they occurred both in systole and diastole. Remembering Hamman's description of interstitial emphysema, the possibility of this diagnosis presented itself. At this time, however, it seemed more likely that the sounds were caused by acute fibrinous pericarditis, even though the "rub" was not quite characteristic. On the following day when the patient was seen the diagnosis was clear, for the characteristic bubbling, crunching, crepitant sounds, described by Hamman, were so distinctive as to admit of no other interpretation. The pain in the chest was much less intense. However, with changes of position the patient could modify the intensity of the curious sounds and also influence the severity of the pain. At certain times the sounds within the chest were heard at a distance of several feet by the patient's mother.

The white blood cells numbered 11,000. The electrocardiogram was normal. By evening the temperature was 99°.

The following morning the bubbling, crunching noises were slightly louder, but the patient seemed more comfortable. The area of absolute cardiac dullness was now completely absent and both sides of the chest were hyperresonant to percussion. The breath sounds were normal except at the extreme left apex, where they were somewhat distant.

On the next morning (the third day following the onset of the pain in the chest) the patient was brought by ambulance to the Holmes Hospital.

On admission the physical findings were described by Doctor F. Post, the resident physician, as follows:

"There is a definite limitation of expansion of the left side. On deep inspiration there were audible and palpable crackles which sound like a piece of newspaper being wrinkled. These sounds are maximum to the left of the sternum at the level of the third rib. Percussion note slightly more booming on the left than on the right. Impossible to obtain cardiac borders of dullness due to the booming percussion note. Heart sounds quite distant. No thrills, murmurs or frictions."

For the first time, slight but definite crepitation was felt in the skin overlying the sternum. This disappeared in 3 hours, and did not recur.

Roentgen ray of the chest was (Dr. H. G. Reinecke) as follows:

"Chest examination reveals a small pneumothorax on the left side with the top of this lung being retracted downward through a distance of 3 to 4 cm. Along the lateral chest wall the collapse is seen to almost the midthorax. No fluid is shown. On the right no pneumothorax is seen. On the lateral view air is seen in the soft parts of the anterior thoracic wall and possibly also in the anterior mediastinum. No air is seen over the shoulder areas or in the soft parts of the neck."

On the third hospital day the crackling sounds had completely disappeared, but on the following day there was a reappearance of the crackles associated with slight pain. At this time it was noted that the pulmonary second sound was greatly exaggerated on both palpation and auscultation.

The following day all abnormal physical findings except for the hyperresonant percussion note had disappeared and the Roentgen ray showed complete disappearance of the pneumothorax and of the air in the mediastinum. The temperature was 99° on the evening of the second day in the hospital; from this time the temperature remained normal. On the tenth hospital day, the patient was discharged from the hospital. After a week of rest at home without symptoms she returned to school and has been entirely well to date. A Roentgen ray of the chest May 5, 1938, showed no abnormalities.

CASE 2.—M. B. (No. 81106), a 39-year-old white American housewife, was transferred to the Medical Service of this hospital from the Obstetrical ward on November 8, 1937, because of the sudden onset of a sharp pleuritic pain in the left chest which began 15 minutes following a difficult labor at which twins were delivered. The patient's past history revealed that she had "growing pains" in the legs at the age of 9, and 18 months before admission had had some vague arthritic pains in the right hip. There had been no fever or tachycardia and she had not been in bed. During the last half of her pregnancy detection of the characteristic murmurs led to a diagnosis of mitral stenosis. There were never any signs of cardiac failure. At this time she had come to the prenatal clinic because of a sore, red tongue. A microcytic anemia with hemoglobin of 8.5 grams and red count of 3.3 million was detected. On a high caloric, high vitamin diet with supplements of brewers' yeast and iron, the tongue returned to its normal condition and the anemia responded well. One month before delivery, twin pregnancy was diagnosed by palpation and confirmed by Roentgen ray.

The obstetrical note reveals that "the membranes were ruptured 5 hours before delivery. The first stage of labor lasted 8 hours; the second, 2 hours; the last, 6 minutes." The labor was extremely difficult for a para VI. Fifteen minutes after delivery, when the patient had returned to the ward, she experienced a sudden, sharp, stabbing pain in the precordial region which radiated directly through the chest to the back, where it was most intense at the region of the inferior angle of the left scapula. The pain was made worse by deep breathing or moving to either side or sitting up. It was relieved but not abolished by a fourth of a grain of morphine. She was seen 4 hours later by the medical consultant, who made a diagnosis of rheumatic heart disease with mitral stenosis and insufficiency, well compensated. The adventitious sounds heard in the precordial region were interpreted as the friction rub of an acute pericarditis and pleuropericarditis, probably on the basis of an acute rheumatic pancarditis. She was then transferred to the medical service.

The physical examination revealed a well developed and adequately nourished white female of 39 years, lying quietly flat in bed and in no pain so long as she remained quite still. Mouth temperature was 99° F., pulse 90, respirations 20, and blood pressure 114/78. The color was good and there was no evidence of shock. Except for enlarged tonsils and lactating breasts the findings of interest were limited to the chest and heart. Inspection revealed respirations which were regular and easy, but shallow. There was a decrease in expansion of the left chest with more pronounced splinting on deep breathing. Both sides of the diaphragm moved equally but the excursion was only moderate. Tactile fremitus was equal on both sides and there was no subcutaneous crepitation anywhere. Percussion elicited no abnormality. There was no evidence of pneumothorax or mediastinal shift. Breath sounds were vesicular and no râles were heard. The apex beat of the heart could be seen and felt in the 5th interspace in the midclavicular line, 7 cm. from the midline, just inside the left border of percussion dullness, which measured 8 cm. on the left and 3 cm. on the right. At times a vibration could be felt in the 3rd left interspace near the sternum.

It was easily obliterated by pressure in the area and this was associated with an alteration in the adventitious sounds. The heart sounds were regular and of good quality. At the apex, the second sound was split and there was a high pitched systolic murmur transmitted to the axilla. There was a low rumbling late diastolic murmur. The second sound at the base was accentuated on both sides, slightly louder in the aortic area. An unusual adventitious pleuropericardial sound, clicking, crunching, grating, but not bubbling, could be heard over most of the precordium, loudest over the second and third interspaces on the left. Though louder in systole, it was audible in diastole. It was heard best when the breath was held in deep inspiration (and this was painful), but was present in every phase of the cardiac or respiratory cycle. The intensity of this sound varied from time to time, being quite loud an hour after the onset of the pain and gradually decreasing for 48 hours. At this time the patient was moved about considerably in the process of taking Roentgen rays. This was associated with a great increase in the intensity of the sounds, and the pain which had markedly diminished came back with increased severity. Following this, the sounds gradually decreased so that they were barely audible on the 5th day after onset, but not thereafter. The Roentgen rays taken on the 3rd and 7th days of the illness did not show any pneumothorax or interstitial emphysema in the antero-posterior, lateral or either oblique views. The leukocyte count varied from 6900 to 10,500 per c.mm. with a normal differential. The urine was negative save for a few epithelial cells and leukocytes. Mouth temperature varied between 98 and 99.8° F., the pulse from 80 to 100, and respirations from 20 to 25.

The patient, seen 3 months following the episode, was quite healthy and normal in every way and had suffered no recurrence of the pain.

Discussion. The mechanism responsible for the auscultatory findings of interstitial emphysema is probably dual. When the air which has escaped along the interstitial connective tissue bands collects beneath the visceral pleura in the region of the heart, blebs are formed and the crunching sounds heard in patients with this disorder have been duplicated by us experimentally in dogs. However, it is highly probable in clinical cases that air having reached the anterior mediastinum finds its way between the spaces of the areolar tissue and when impinged upon by cardiac contractions causes crepitation.

These cases illustrate very clearly the essential clinical picture of this syndrome. In the second case, the onset came shortly after the severe strain of labor. In the other case, symptoms occurred while the patient was engaged in a very mild form of exercise involving no strain whatsoever. In neither case was there any clinical evidence of serious constitutional disturbance commensurate with the auscultatory signs, no shock, no cyanosis, no sweating and no tachycardia. Both cases, interestingly enough, were females, while all of Hamman's were males. In both cases the diagnosis was made by detection of the crunching, crackling, bubbling sounds and pain over the heart. We believe that it should be stressed that these sounds show great spontaneous variation in quality and intensity during the progress of the illness and may not be characteristic at all times. They also vary with change in position of the patient. In these

TABLE 1.—CLINICAL DATA IN RECORDED CASES OF SPONTANEOUS INTERSTITIAL EMPHYSEMA OF THE LUNGS.

	Hamman, Case 1.	Hamman, Case 2.	Hamman, Case 3.	Hamman, Case 4.	Hamman, Case 5.	Hamman, Case 6.	Lister, Case 7.	Wolferth and Wood, Case 8.	This series, Case 1.	This series, Case 2.
Age	51	17	25	35	29	16	31	21	17	39
Sex	M	M	M	M	M	M	M	M	F	F
Color	W	W	W	W	W	W	W	W	W	W
Temperature	N	101.2	99.4	N	.....	Diabetic coma	N	.....	99.0	99.8
Pulse	N	.....	.....	.....	.....		116	.....	96	96
Respirations	N	.....	.....	.....	.....		.....	.....	20	20
Blood pressure	N	.....	.....	.....	.....	.....	145/90	.....	130/80	114/78
White blood cells	N	13,000	N	N	.....	28,500 to 5000	.....	.....	11,000	6900 to 10,500
Pain	Severe in chest	Severe in neck and chest. Painful swelling	Sharp in left side of chest	Very severe in left chest	Very severe in left chest	Severe in right lower chest	Severe in upper chest	Pain in chest on exertion	Moderate in left anterior chest	Very severe in lower left chest
Duration	Bad for ½ hour. Several days	Fever 1 day	8 days	3 days	Few days	Few days	3 weeks	2 days	6 days	5 days
Onset	Shaving	Sitting in chair after	.....	Getting out of a car	Walking on street on cold day	In bed	Sitting in a train car	While wrestling	Standing dribbling basket-ball	In bed 15 minutes after delivery
Sounds	Crunching, bubbling	Systolic, crunching	Loud, moist, crackling and crepitant systolic noise	Crackling sound with each systole	Crackling, clicking sounds varying with each systole	Crackling, popping sounds over the sternum	Hollow, knocking sound similar to that over brachial artery when taking B.P.	Heard across the room	Like wrinkling of a newspaper	Clicking, crunching, grating sound in chest and 2d and 3d left interspaces
Trepopnea	.....	Sitting up	.....	Sitting up	.....	.....	.....	.....	Right side	Flat on back
Decrease in cardiac dullness	0	.....	.....	0	Marked	.....	.....	.....	Marked	0
Subcutaneous emphysema	0	+	0	0	0	+	+	0	Small transient over sternum	0
Electrocardiogram	Low potential, but otherwise normal	.....	.....	Low voltage in L_1; diphasic T waves II	.....	.....	.....	.....	Normal	Normal on 3d and 7th days
Intrathoracic sounds heard by patient	Synchronous with the heart beat	.....	Synchronous with the heart beat	In region of the heart	.....	.....	Synchronous with the heart beat	Synchronous with the heart beat	In the region of the heart	0
Sounds heard best with patient	On left side	.....	On left side. Disappeared on sitting up	Only with the patient flat on his back	.....	.....	Standing or sitting, absent with patient flat on back	.....	In any position	In any position
Roentgen ray	N	.....	N	Early infiltration at apices	Small left pneumothorax	Air in mediastinum between anterior chest wall and heart	Left pneumothorax	Small left pneumothorax	Air in mediastinum lateral view	Negative
Pneumothorax	0	0	0	Small, left	Small, left	0	Large, left	Small, left	Small, left	0

respects they are like the notoriously fickle pericardial friction rub after coronary occlusion. Apparently the break in continuity of the air passages may close temporarily and open again, allowing more air to escape into the interstitial tissues, thus producing changes in physical signs. Any increase in the sounds is apt to be associated with an exacerbation of the pain.

These cases may exhibit trepopnea and both patients in this report preferred to lie flat in bed. Since movement may increase the pain, the patients prefer to remain very quiet. Respiratory motions may be limited on the side where the pain is greatest. Such activities as coughing and sneezing may be agonizing and are strongly resisted.

In the first case there was complete obliteration of the area of cardiac dullness. Roentgen rays revealed a small collection of air between the heart and anterior chest wall and a small pneumothorax on the left. It may be of some significance that when pneumothorax has been encountered, it has been on the left side.

Subcutaneous emphysema was detected at no time in Case 2, though diligent search was made on repeated occasions. In the first case it would have been missed without repeated search, as it was very small in amount and had disappeared within 3 hours. Neither of the cases had air in the subcutaneous tissues above the clavicles.

Recently there was a patient on the medical wards in whom a not infrequent accident consequent upon thoracentesis gave confirmatory evidence to the suggestions made by Hamman regarding the pathogenesis of this condition. During the procedure the lung was punctured by the needle and a pneumothorax was induced. The patient soon called attention to a curious noise emanating from his chest. Slight pain was present in the chest. The sounds were audible to the naked ear 2 feet from the chest wall and on auscultation one could hear the typical grating, grunting and crunching sound, which was very loud. There was no subcutaneous emphysema and in 2 days the sounds were no longer to be heard. Roentgen ray confirmed the diagnosis of pneumothorax but did not reveal a mediastinal emphysema. This clearly illustrates that the signs appearing in spontaneous interstitial emphysema of the lung may be produced artificially by puncture of the lung. Such an event occurring spontaneously may give rise to nothing but a pneumothorax. We feel, however, that escape of air into the interstitial tissues of the lung is by no means rare and that if all cases with spontaneous pneumothorax were examined carefully, the typical sounds described above would be found frequently. In many cases, the patient calls the attention of the physician to the curious noises within the chest.

Differential diagnosis must be made between this condition and coronary thrombosis, pneumonia, pulmonary infarction and pericarditis. The finding of the unusual precordial sounds in a patient

with severe pain and the absence of other signs commensurate with the symptoms should lead one to make the diagnosis. Roentgen ray may reveal the air in the mediastinum, or subcutaneous emphysema may appear to substantiate it. Because of the benign nature of the condition, patients may be reassured and spared unnecessary invalidism.

Treatment should be conservative and palliative. Unless there is extensive subcutaneous emphysema, there is no reason to use 95% oxygen as advised by Fine, Hermanson and Frehling.[2]

Summary. 1. Two cases of Hamman's Disease (spontaneous interstitial emphysema of the lung) are described.

2. The syndrome results from the rupture of alveoli, or small bronchioles, the escape of air from its normal pathways within the lung, its dissection along interstitial bands and passage into the anterior mediastinum.

3. Criteria for the diagnosis are: Sudden onset of pain in the chest with bubbling, crunching sounds heard over the heart. Additional signs are: Decrease in the area of cardiac dullness, evidence of air in the mediastinum by Roentgen ray examination of the chest in the lateral position, and pneumothorax, especially of the left side.

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THE INCIDENCE OF THE VARIOUS TYPES OF GASTRIC DISEASE AS REVEALED BY GASTROSCOPIC STUDY.

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Statistics on the various types of gastric disease based solely on gastroscopic observations necessarily must have fundamental disadvantages. Not every patient suffering from epigastric distress is subjected to gastroscopy, even not if gastroscopy is considered to be a very important method of examination for these patients. This statement especially refers to duodenal ulcer. Usually gastroscopy is preceded by Roentgen ray, and by careful Roentgen ray relief study almost every duodenal ulcer can be demonstrated. If

by Roentgen ray examination the niche of a duodenal ulcer has been found, often gastroscopy may appear unnecessary. The same is true of some cases of gall bladder disease. Nevertheless, gastroscopy reveals many diseases which cannot be found by any other method. Therefore it seemed to us to be worthwhile to compile the findings of all patients examined with the flexible Wolf-Schindler gastroscope. Such a compilation not only gives an idea about the percentual distribution of gastric diseases, but also permits comparison of the incidence of gastric diseases in Europe (Munich) and in the United States (Chicago), since 335 gastroscopies in 255 patients were carried out in Munich, and 1691 gastroscopies in 1000 patients were carried out in the United States, most of them in Chicago.

Evidently the quality of such a material does not depend only upon geographical factors. Personal and occasional factors may play an important rôle. This is particularly true if low figures are used, and for this reason no statistical summary was attempted before 1000 patients had been examined gastroscopically.

The incidence of *acute* gastric disorders cannot be determined from gastroscopic observation, since there is no indication for gastroscopic examination in acute gastritis, in some forms (corrosive gastritis, phlegmonous gastritis) gastroscopy even being contraindicated.

Lack of certain material may also influence the statistics. Alterations of the gastric mucosa probably are not infrequent in pulmonary tuberculosis; however, patients suffering from tuberculosis rarely are referred for gastroscopy. The same is true of colitis and appendicitis, although according to recent observations severe gastritis may be combined with these diseases (Royer, Bur, Montejano.[6]) Perhaps still more important is the lack of skin diseases, allergic diseases and certain blood diseases in our statistics. The French school, especially P. Chevallier and Moutier,[2] have shown that many kinds of alteration of the gastric mucosa occur in chronic skin diseases, such as eczema, urticaria, and others. It seems that atrophic gastritis in such conditions is frequent in accordance with older dermatologic conceptions. However, this type of disease is missing in our material. The same is true of gastric allergy. Allergic manifestations of the gastro-intestinal tract have often been assumed; their presence has been proved by careful gastroscopic observations by R. Chevallier.[3] I have not had the opportunity to gastroscope patients suffering from allergic gastro-intestinal symptoms. In most blood diseases definite changes of the gastric mucosa are present, and our material contains many cases of pernicious anemia, but not many of severe secondary anemia or leukemia.

Some gastric diseases are so rare that they are not encountered even in 1000 patients, as for instance, gastric tuberculosis, anthrax and actinomycosis. Finally there may be gastric disease without

gastric symptoms. We have reason to believe that diffuse atrophic gastritis may have general symptoms such as tiredness, weakness, and so on, rather than gastric symptoms, and that therefore such patients are not subject to gastroscopy.

Race of the patient does not seem to play a great rôle. In immigrants of all European nations the same diseases were found. Our experience with members of the colored races is not yet extensive enough to permit a definite statement.

One thousand patients were examined in the United States; 733 of them were referred by the various departments of Billings Hospital, University of Chicago, the majority from the gastro-intestinal service of Dr. W. L. Palmer. About two-thirds of them were out-patients. None of them was hospitalized for the gastroscopic examination. One hundred and eighteen patients were examined at Cook County Hospital, Chicago, all of them being in-patients. The same number (118), were examined at Michael Reese Hospital, Chicago, most of them being out-patients; 17 colored patients were referred by the Gastro-intestinal Department (Dr. L. Berry) of the Provident Hospital, Chicago; 6 patients were examined at the Cincinnati General Hospital (Dr. Leon Schiff), 4 patients were examined at the Indianapolis General Hospital (Dr. M. Light), 3 at Oak Forest, Illinois (Dr. J. Eisemann), and 1 at St. Mary's Hospital, Chicago.

In the following table the incidence of the diseases found has been listed. Often several diseases were found in 1 patient. In these instances the case was classified under that disease which usually is considered to be the chief disease. For instance, cases in which ulcer plus gastritis or carcinoma plus gastritis or ulcer plus pigment spots were found were classified as ulcer or as carcinoma respectively (Table 1).

Comment. 1. Under the heading "*Normal stomach*" are included: Psychoneuroses, cases of duodenal ulcer without visible inflammatory or circulatory changes, gall bladder diseases and other organic diseases. The number of these cases is not known.

2. Hemorrhages lying in a normal mucosa cannot be classified under inflammation, as I have repeatedly pointed out. The mucosal hemorrhages seen in generalized purpura are entirely similar to those found in ulcer-bearing stomachs or otherwise lying in a normal mucosa sometimes combined with pigment spots or hemorrhagic erosions. Therefore, we have classified these three phenomena as "localized gastric purpura." In 1 case profuse gross gastric hemorrhage was observed.

3. Most *gastric ulcers* were observed over a period of months or years by repeated gastroscopies (up to 28). A few gastric ulcers demonstrated by Roentgen ray were not found gastroscopically. If they would be added, the total incidence of gastric ulcers would rise to about 7.7%.

4. *Sequelæ of ulcer* are called: benign obstruction of the pylorus,

scars, formation of hour-glass stomach, and perigastric adhesions, the latter being proved by distortions of the stomach and other alterations of shape.

5. There are probably two different entities of *chronic non-specific gastritis* which should be listed separately: the superficial-atrophic form and the hypertrophic form.

TABLE. 1.—INCIDENCE OF GASTRIC DISEASES AS FOUND BY GASTROSCOPIC EXAMINATION OF 1000 PATIENTS IN THE UNITED STATES.

		Percentage.	Number of patients.
Normal stomach		22.2	222
Mucosal hemorrhages, pigment spots and hemorrhagic erosions of non-inflammatory origin (localized gastric purpura)		5.6	56
Gastric ulcer		7.1	71
Sequelæ of gastric ulcer		1.4	14
Chronic non-specific gastritis:			
(*a*) Chronic superficial gastritis	*11.0*		
(*b*) Chronic atrophic gastritis	*13.6*		
(Superficial plus atrophic gastritis)	24.6		
(*c*) Chronic hypertrophic gastritis	*17.2*		
Total chronic non-specific gastritis	41.8	41.8	418
Gastric syphilis		0.3	3
Gastric lymphogranuloma (Hodgkin's disease)		0.2	2
Benign tumors		2.2	22
Gastric carcinoma		7.7	77
Lymphoblastoma		0.1	1
Congenital diverticula		0.3	3
Diaphragmatic hernia		0.2	2
Postoperative stomach		8.0	80
Accidents		0.3	3
Examinations attempted, but not successful		1.4	14
Examinations made, but not satisfactory		1.2	12

a. Three of the 110 cases of *superficial gastritis* were seen in duodenal ulcer, 3 in cholangitis, 4 followed therapeutic Roentgen ray irradiation (high voltage Roentgen ray therapy); 1 case was observed in alcoholic pellagra. Five times the diagnosis of a superficial *hemorrhagic* gastritis was made, five times that of superficial *erosive* gastritis, and five times that of superficial hemorrhagic erosive gastritis. A superficial *aphthous* gastritis combined with aphthæ of the mouth was seen in 2 instances. In this series no gross hemorrhage occurred in superficial gastritis.

b. Under "*Atrophic Gastritis*" also those cases were classified which showed a combination of superficial with atrophic changes. In 38 of the 136 cases of atrophic gastritis, superficial gastritis was also present. The frequency of this combination proves the close relationship between these two conditions. They constitute together Faber's chronic progressive pangastritis. Of the cases of atrophic gastritis 15 were seen combined with pernicious anemia, 1 combined with cord degeneration, and 1 combined with tropical sprue. One case of atrophic gastritis was observed in a patient suffering from duodenal ulcer, 2 in patients suffering from cholecystopathy, 1 in a patient who had had lymphatic leukemia, 1 combined

with tuberculosis of the lungs, and 1 combined with acute appendicitis. In 13 cases an atrophic hemorrhagic gastritis was found; but in only 3 instances were *erosions* seen. One atrophic erosive gastritis was found in the patient who suffered from acute appendicitis. In 2 instances severe *gross hemorrhage* was observed.

5. Chronic *hypertrophic gastritis* probably is a clinical entity, although some cases may be related to the atrophic type. In 11 of the 172 cases the diagnosis of hemorrhagic hypertrophic gastritis was made, indicating that mucosal hemorrhages were seen gastroscopically. In 12 cases *ulcerations* of the inflamed mucosa were observed and consequently the diagnosis of ulcerative hypertrophic gastritis was made. In 5 instances hemorrhages plus ulcerations were seen. Four times *gross hemorrhage* was found to originate from hypertrophic gastritis; in 1 of these cases continuous parenchymatous oozing of blood was observed gastroscopically. Ten cases were found in patients suffering from duodenal ulcer, 1 case, respectively, in a patient with lymphogranuloma inguinale and uremia.

6. The diagnosis of gastric *syphilis* was made when *a*, an inflammatory or tumor-like thickening of the gastric mucosa with or without formation of ulcerations was observed gastroscopically; *b*, the Wassermann test was strongly positive, and *c*, the changes observed disappeared after antiluetic treatment.

7. A tremendous thickening of all folds was found in 1 case of *Hodgkin's disease*, while the second one presented the picture of ulcerative hypertrophic antrum gastritis.

8. In 20 instances the *benign tumors* were considered to be epithelial tumors, probably benign adenomas. In 3 cases they were found in pernicious anemia; in 2 instances severe gross hemorrhage—apparently due to the polyps—was observed. In 2 cases the appearance of the tumor was that of a submucosal one, probably of a myoma. Both patients were referred for gastroscopic examination because of gross hemorrhage.

9. Carcinoma of the stomach was usually found easily gastroscopically except, *a*, the case in which obstruction at the cardia rendered examination impossible; *b*, 1 case in which hour-glass formation and 1 in which invagination through an enterostomy stoma prevented visualization of the lesion; and *c*, 2 cases of extensive scirrhous carcinoma in which little could be seen, although the diagnosis could be made because of the lack of distensibility of the stomach. This good result contrasts with the results of other gastroscopists. Important information was obtained bearing on the macroscopic type of tumor and upon its operability. Borrman's[1] simple classification of gastric carcinoma according to their macroscopic appearance has been proved to be valuable. The very favorable, sharply limited polypoid Type 1 carcinoma was found in only 2 instances. The Type 2 carcinoma, the localized malignant ulcer, surrounded by a sharply limited wall, was encountered 12 times. The Type 3 carcinoma gives a very dubious prognosis; it is a malig-

nant ulcer, walled off only on one side of the ulcer; it was seen in 11 cases. The unfavorable diffusely infiltrative Type 4 carcinoma was observed in 43 instances. In 5 cases a carcinoma of the cardia was visualized gastroscopically. Gastroscopy proved to be especially valuable in differentiating benign and malignant ulcers. In 3 of the 77 cases gastroscopically examined, a carcinoma was diagnosed at a time at which clinically and roentgenologically a benign ulcer was believed to be present. In all 3 cases the Roentgen ray niche apparently became smaller under treatment, but in every instance operation or autopsy proved that the gastroscopic diagnosis had been correct.

10. The case of *lymphoblastoma*, the third to be observed gastroscopically, has been described by Renshaw.[4]

11. Two of the 3 *congenital diverticula* observed occurred in syphilitics. They had, however, the outspoken appearance of a congenital lesion.

12. *Hernia Diaphagmatica.* At two examinations the gastroscope entered the stomach. One of the 2 patients was examined repeatedly, but usually only the supradiaphragmatic portion of the stomach became visible.

13. Gastroscopy was carried out in 29 resected stomachs, in 50 patients having a gastroenterostomy, and in 1 patient having had a pyloroplasty. In this latter, a gastritis of the postoperative stomach was found. In the other groups, the findings were as follows:

Resected Stomach. An entirely normal stomach was found in 3 instances. In 2 of them the stoma showed the rare picture of rhythmical pylorus-like contractions. (We should not forget that usually only patients suffering from distress were observed). In 2 instances mucosal hemorrhages of the normal mucosa were found (virtual ulcer stomach, see p. 511). Jejunal or marginal ulcers were found in 4 cases, but no recurrent ulcers were seen in the stomach proper in this group. Gastritis of the postoperative stomach was found in 16 instances, jejunitis plus gastritis twice. Recurrent carcinoma was present in 2 cases, but visible only in 1 of them.

Gastroenterostomy. The stomach was found to be normal in 6 instances, in 3 of which rhythmical function of the stoma was observed. In 1 case mucosal hemorrhages of the normal mucosa were seen. Jejunal and marginal ulcers were seen 5 times, recurrent gastric ulcers twice. In 1 case, obstruction of the jejunum below the opening was diagnosed from the rhythmical ejection of white bismuth powder through the stoma from the intestine into the stomach. This diagnosis was confirmed by operation. Silk sutures (always combined with gastritis or erosions) were seen in 4 cases. Gastritis was found 30 times. A gastro-colic fistula was present once. The old opinion of all gastroscoping clinicians that a severe gastritis is the most important disease of the postoperative stomach was confirmed.

14. The three *accidents* occurring with the flexible gastroscope

have been described elsewhere. They were non-fatal perforations of the gastric wall and they happened within a very short period of time, during gastroscopies Nos. 713, 771 and 781 (June 30, 1935 to September 12, 1935). It was possible to prove experimentally[8] that they were due to a modification of the standard tip of the gastroscope, the so-called "rubber-sponge." Since returning to the use of the rubber finger tip, there have been no accidents to date in over 1323 examinations.

15. *Examinations attempted but not successful* include those in which the attempt of a gastroscopic examination was made, but did not succeed. The reasons thereof were: Non-coöperation of the patient, 5 times; unexpected lesions of the cardia, 8 times; food remnants, once.

16. *Examinations* made but considered *unsatisfactory* were those in which the introduction of the gastroscope was possible, but important portions of the stomach, especially its distal parts, were hidden from view. The reasons (12 cases) were: Non-coöperation, 3 times; continuous spasms, once; obesity, once; food in the stomach, twice; barium in the stomach, twice; distention of the stomach impossible because of leather-bottle formation, once; distortion of the stomach from adhesions, once; kyphosis, once.

Finally, diagnostic errors must be considered. No diagnostic method probably is free of the possibility of error. And if errors are frequent they may influence the statistical results. The number of mistakes in gastroscopy depends largely upon the experience of the examiner. To the best of our knowledge the following mistakes were made: Six ulcers located in the so-called blind areas of the stomach were not found. These are not "wrong diagnoses," since knowledge of the gastroscopic method presupposes the presence of these blind areas and assumes that localized lesions of these areas cannot be found gastroscopically. Perhaps this disadvantage can be diminished by further development of the method (Rodger's sheath.[5]) One carcinoma of the postoperative stomach was not seen because of overlapping invaginated mucosa. In 1 case a hemispherical protuberance of the antrum was described; autopsy in this case revealed a carcinoma of the pancreas. In 2 cases the differential diagnosis between infiltrative carcinoma and hypertrophic ulcerative antrum gastritis was impossible. In 1 of them, in which I was inclined to diagnose a carcinoma an antrum gastritis was found, in the other 1 antrum gastritis seemed to be more likely, but carcinoma was found. Possibly other mistakes were made which were overlooked, in spite of the attempts to check every case. Therefore, no figure for wrong diagnoses can be given.

It has been contended that the incidence of gastric diseases in Germany differs from that in the United States (Walters and Sebening[9]). Therefore, German statistics shall be given, though based on a smaller material. In a specialized gastro-intestinal practice in Munich 335 gastroscopies were carried out in 255 patients from

1932 to 1934. The Wolf-Schindler flexible gastroscope was used. The findings are given in Table 2.

TABLE 2.—INCIDENCE OF GASTRIC DISEASES AS FOUND BY GASTROSCOPIC EXAMINATION OF 255 PATIENTS IN GERMANY.

		Percentage.	Number of patients.
Normal stomach		24.3	62
Mucosal hemorrhages, pigment spots and hemorrhagic erosions of non-inflammatory origin (localized gastric purpura)		8.25	21
Gastric ulcer and sequelæ of ulcer		8.6	22
Chronic non-specific gastritis:			
(*a*) Chronic superficial gastritis	12.0		
(*b*) Chronic atrophic gastritis	19.0		
(Superficial plus atrophic gastritis)	31.0		
(*c*) Chronic hypertrophic gastritis	14.0		
Total chronic non-specific gastritis	45.0	45.0	115
Benign tumors		1.6	4
Carcinoma		7.85	20
Postoperative stomach		3.2	8
Examinations attempted, but not successful		0.8	2
Examinations made, but not satisfactory		0.4	1

The difference between the two statistics is so slight that it almost is unnecessary to discuss it. However, although the proportion of chronic gastritis is about the same in Munich as in Chicago, the distribution of the two great groups is a different one: In Chicago the percentage of superficial-atrophic gastritis is 24.6%, in Munich 31%. In Chicago hypertrophic gastritis is 17.2%, in Munich 14%. No cases of ulcerative antrum gastritis were seen in Munich. The incidence of "localized gastric purpura" was higher in Munich than in Chicago (8.25% to 5.6%). The ulcer figures (8.5% to 8.6%) and the carcinoma figures (7.7% to 7.85%) were about the same. The higher incidence of postoperative stomachs in Chicago is noteworthy (8.0% to 3.2%). The smaller figure of impossible and unsatisfactory examinations in Munich is easily explained by the fact that in Munich all patients were private patients seeing the doctor of their own choice and therefore being confident and quiet.

Summary. 1. Statistics on the incidence of gastric diseases in the United States and in Europe are presented, based upon gastroscopic findings in 1000 and in 255 patients.

2. There are apparently no outspoken geographical differences in the distribution of gastric diseases.

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A REVIEW OF A FIVE-YEAR TUBERCULOSIS PROGRAM AMONG UNIVERSITY OF WISCONSIN STUDENTS.

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Quoting from the 4th verse of the 16th chapter of St. Matthew—"A generation seeketh after a sign and no sign shall be given unto it"—the proposition as concerns disease and especially tuberculosis in its early stages is well expressed. For many centuries pulmonary tuberculosis has been associated with certain common and well known symptoms. Considering early diagnosis this association has been unfortunate, for usually the minimal and not infrequently the moderately advanced stages occur without symptoms. Even the far advanced stage has not produced symptoms sufficient in degree to prevent 4 students—unaware of their active tuberculosis—from enrolling in the University during the past 5 years. The association of symptoms and tuberculosis offers an adequate explanation why, according to a recent survey (1935) of the American Medical Association,[1] only 13.1% of 66,861 patients were admitted to sanatoriums in the minimal stage, while 29.7 and 57.2% respectively were in the moderately advanced and far advanced stages. Compared to the earlier surveys by Drolet[5] (1926) and Whitney[7] (1931), no progress as regards earlier diagnosis has been made. Because treatment early in the disease is undoubtedly the biggest factor in recovery, it is unfortunate that late diagnoses are still the rule. An efficient and well directed tuberculosis program would make possible the discovery of more than 70% of all cases while still in the minimal stage. Today, unfortunately, and of necessity, the time and energies of sanatorium physicians must be directed to caring for the large proportion of patients who have far advanced tuberculosis—cases which emphasize the futility of treatment late in the disease.

Medical practice in the past has been hampered by the lack of a general public interest in health and medical efforts for its maintenance. Without the technical assistance of Roentgen ray and the laboratory, physicians necessarily had to be content to study the pathologic process after it had reached a stage sufficient to produce symptoms and clinical signs. Usually in the study of pathologic processes we first learn and recognize disease in its late or end stages as presented at the bedside or postmortem table, and relatively speaking know little of the manifestations of early disease when treatment is most effective. Since the presence of early disease can be determined in many instances only by laboratory means, it is evident that the methods of approach must change. With a rapidly growing appreciation by the layman of the value of disease

prevention and earlier discovery, the importance of an annual medical examination will be more widely recognized. This offers the physician a great opportunity, and he should not be content to let this important examination consist of a physical examination and a pat on the back with the assurance that everything is all right. Good medical practice in the future will demand more. Urine analysis will consist of more than the examination of a single specimen. Urine collected during a 24-hour period will be examined for sugar, albumin, pus and blood. Chemical analysis of the blood for sugar will be done to diagnose diabetes not yet severe enough to cause symptoms. Laboratory tests can determine the function of the kidneys and the heart, and Roentgen ray examinations of the teeth, sinuses, bones and lungs will in many instances discover disease not known to exist. Special examinations of the gastro-intestinal tract frequently would reveal latent disease, and microscopic examination of tissues might prove or disprove a diagnosis. Today we make little effort to find a pathologic process until it produces symptoms, and, therefore, have much to learn as to the origin and pathogenesis of early disease. When the apparently healthy present themselves for study, the medical profession should be sufficiently informed and interested to give an adequate health examination.

A student health department, dealing with apparently healthy individuals, is at once met with the challenge as to whether all individuals matriculating in college are in fact healthy and physically capable of carrying the burden of a college course. Allowing a student with a clinically latent but pathologically active disease process to do his work without close medical supervision is obviously dangerous. In the past, health examinations have consisted primarily of a history, physical examination and a single examination of the patient's urine. That with further special studies much more can be determined as to the student's status is well illustrated by this survey of pulmonary tuberculosis—a disease frequently found among the college age group.

Tuberculous Infection. The diagnosis of minimal pulmonary tuberculosis is dependent on repeated examination of the apparently healthy for tuberculous infection and disease. The success of dairymen in many states in reducing infection among cattle to less than 0.5% suggests the value of a similar effort among humans. Much money and energy has been and is being expended in treating the 87% with moderately and far advanced disease. Relatively little has been done to find and treat the process while it is still in the minimal stage. The potentialities of a tuberculosis program to include the general population are suggested by the results of a 5-year survey among University of Wisconsin students.

All students enrolling for the first time in the University are given as part of their entrance health examination a tuberculin test.

Those showing no reaction to 0.005 mg. of standardized tuberculin (Purified Protein Derivative of Seibert and Long) are regarded as free of tuberculous disease* and in most instances of tuberculous infection. To date, no case of pathologically active tuberculosis has been discovered in an individual having a negative Mantoux test to 0.005 mg. P. P. D. or to 1.0 mg. Saranac Lake Laboratory Old Tuberculin. During the 5-year period over 16,000 students have enrolled in the University for the first time. Students enrolling in September totaling over 15,000 have been tested by the 2-dose method. A smaller group numbering over 1000 enrolling at the beginning of the second semester were tested with the single stronger dose—0.005 mg. P. P. D. It was found that with the 2-dose method, the total percentage of 3 and 4 + reactors was 3.7 and 0.24% respectively, compared to 8.6 and 1.5% when the single strong dose was used. Otherwise stated there were 2.3 times as many 3 + reactors and 6 times as many 4 + reactors when the single strong dose was used. Though no ill effects other than a very sore arm, accompanied in certain cases by constitutional symptoms, have been noted, the 2-dose method is preferable. If only one dose of tuberculin is given, the examiner should appreciate the fact that unless the stronger strength dose is used—either 0.005 mg. P. P. D. or 1.0 mg. O. T., all active cases of tuberculosis will not be found. Of the 71 active cases discovered in the 5-year period, 16 (22.5%) failed to react to the weaker dose. Of the 16 not reacting to the weaker dose, 5 had suspicious positive reactions to the first test, but without edema approaching 5 mm. The single strong dose method is not advocated; but since in many case finding programs the single weak dose alone is used, the fact should be emphasized that by this method in our study only 57% of the infected would have been determined, and all of the active cases would not have been found. Where the 2-dose method was used, 16.23% (57% of total positive) reacted to the first strength P. P. D. and an additional 12.24% (43% of total positive) reacted to the stronger dilution.

Where large numbers are concerned, the yearly increase of infection in the age groups from 16 to 25 is shown in Table 1. The possible reasons for the rapid increase from 19.4% to 50% in this 10-year period are of interest. Certainly in this stage of life the individual leaves his rather limited home circle. His acquaintances and contacts increase, he covers a wider geographic range; and his social habits further the possibility of infection. The frequency with which tubercle bacilli are found in minimal tuberculosis by special examination[6c] suggests that these asymptomatic cases may be infectious to others by kissing or mouth to hand contact.

Summaries of the Mantoux tests by ages (Table 1) indicates a con-

* Roentgen ray study of a group of students negative to 0.005 mg. P. P. D. revealed that 6% had calcified lesions in the lungs or hilum glands.

sistently smaller infection rate among women. The total number of infected, though showing a yearly variation of only 2.75% in the years 1933 to 1936 inclusive, with an average yearly infection rate of 28.5%, showed a marked decrease in 1937 to 23.3%. Whether the most recent figure will serve as an indicator pointing to a lower infection rate in the future will be of notable interest.

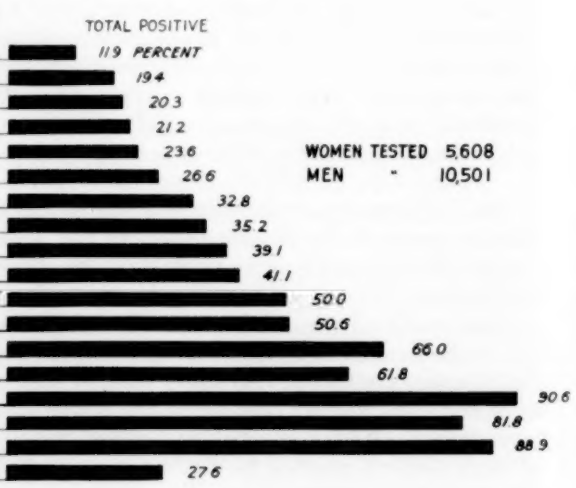
The geographic variation of infection among students from different sections of the country is shown in Figure 1. The higher infection rates of students coming from the East are consistent with

TABLE 1.

TUBERCULOUS INFECTION

MANTOUX TESTS OF 16,109 STUDENTS FIVE YEARS 1933-1938

AGE	NO. TESTED	PERCENT + WOMEN	PERCENT + MEN
10-15	106	11.9	17.2
16	139	18.5	19.7
17	1438	18.9	21.9
18	4735	19.5	22.4
19	3240	21.2	24.9
20	2130	26.6	26.6
21	1324	25.8	35.1
22	922	29.4	42.9
23	514	44.3	38.2
24	392	43.8	40.0
25	234	44.0	54.6
26-30	591	44.3	54.2
31-35	203	61.7	68.9
36-40	89	58.1	65.2
41-45	32	94.1	86.7
46-50	11	71.4	100
51-56	9	80.0	100
TOTALS	16,109	24.1%	29.5%



PPD WAS USED IN ALL BUT 1987 STUDENTS TO WHOM SARANAC LAKE OT WAS GIVEN
FAILURE TO REACT TO 10 mg O.T. OR 0.005 mg PPD CONSIDERED NEGATIVE

the infection rates found in Eastern colleges.[2] Only the mountain states approximate the low infection rate of the north central area. The high infection rate of Arizona and New Mexico is indicative of the probability of infection of those living with the tuberculous. Two University of Wisconsin students, spending a winter in Tucson, Arizona, negative on leaving, were positive on return. Infection rates among students from the Southeast are uniformly high, and approach the rates of those from the East.

As to infection rates among urban and rural groups, it is of interest to note that of all students tested, those coming from rural Wisconsin and enrolled in the short course in Agriculture show the smallest

incidence of infection. Of 742 students tested, 175 (23.6%) were positive. In no instance to date has a case of pathologically active tuberculosis been found in this group.

Though the numbers are not large and, therefore, offer no proof, they suggest a correlation between the infection rates of students and the death rates of the county or section of the state from which they come. Infection by counties is presented in Figure 2. The Wisconsin tuberculosis death rate per 100,000 population for the 8-year period from 1930 to 1937 was 41.8.* Of Wisconsin's 72 counties, 13 have death rates above the state average. The northern-

FIG. 1.

most tier of counties, 8 in number, and 2 counties adjacent contain 10 of the 14 counties having the highest death rates in the state. No other combination of an equal number of Wisconsin counties has such a high infection rate as these 10 northern counties. The most heavily populated areas of the state, Milwaukee, Racine and Kenosha counties, also show a high infection rate. The death rate of Milwaukee County ranks seventh among the counties, while the rates of Racine and Kenosha counties are below the state average. The high infection rates of Winnebago and Jefferson counties from which relatively large numbers of students were tested cannot be explained on a basis of death rates.

* Statistics of the Wisconsin Anti-Tuberculosis Association and Wisconsin State Board of Health.

Differences of opinion exist as to the benignity of lesions produced by first and reinfection. The fact that more tuberculosis has occurred among nurses previously non-infected than in the infected suggests that the first infection may have produced a progressive pathologic process which may eventually result in death to the individual.

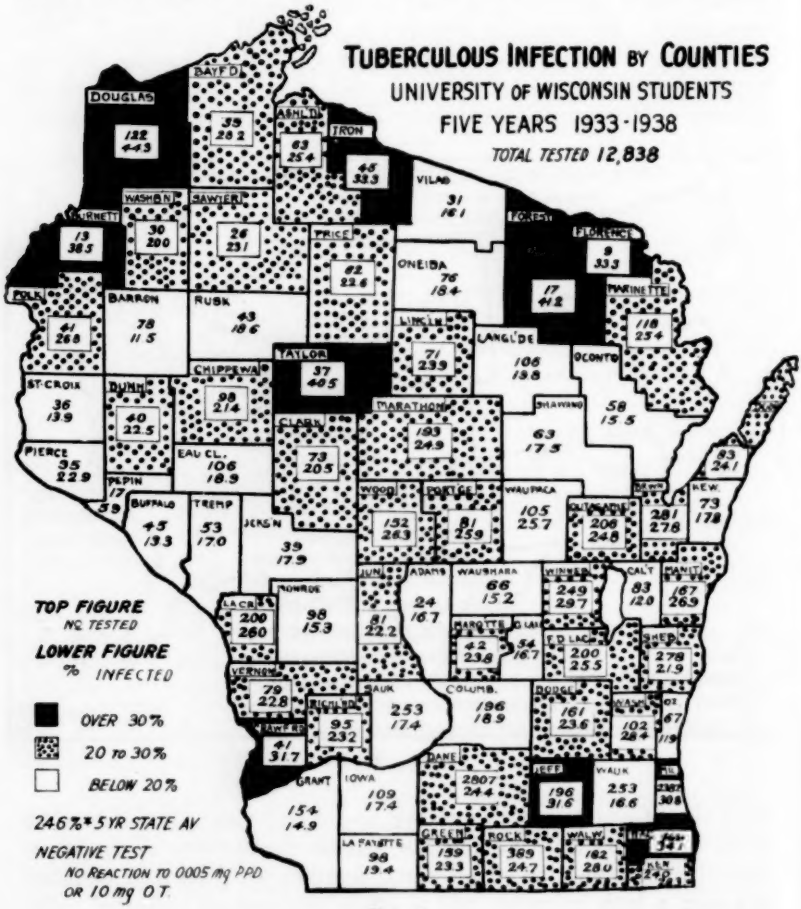


FIG. 2.

Many have concluded that the infected group have developed a relative immunity because of their infection. This may be the answer in part, but another circumstance requires consideration. The infected group no longer contains those who may have developed progressive disease from their first infection. Individuals infected for a considerable period of time without the development of progressive tuberculosis may be considered as a group who have proven their inherent resistance which may have been further enhanced

by the first infection. The non-infected have not established their status. From evidence at hand it appears that progressive tuberculosis may develop from the first infection. Close observation of the pathologic process following the known time of infection will alone answer the question.

Myers and his co-workers[4] are of the opinion that the first infection occurring in either childhood or adult life is benign and requires no treatment. Some of their conclusions follow:

"The first infection type of tuberculosis as observed in our group of adults has resulted in no significant symptoms or abnormal physical signs throughout the entire course of development. Indeed the lesions in the majority of our cases would not have been known to exist had it not been for periodic tuberculin testing and the making of Roentgenograms of the positive reactors.

"In our experience, adults in whom the first infection type of tuberculosis develops, even with considerable involvement in the pulmonary parenchyma and regional lymph nodes, do not require treatment in any form.

"Apparently it makes little or no difference at what time of life the first infection with tubercle bacilli occurs, with reference to the evolution of tuberculosis in the human body. When the first infection type of disease occurs in the second and third decades of life, it is just as benign as when it occurs in childhood."

Our experience in 4 cases of students recently infected has been very different from that of Myers. Two students developed cavitation from lesions, as indicated by the sequence of events, resulting from first infection. Both subsequently developed symptoms and physical signs, and after 1 and 2 years of treatment respectively are still in sanatoriums. Another, after 2 years of treatment returned to the University this past semester, and tubercle bacilli continued to be present in her gastric contents, though her pulmonary lesion had receded in size. A student nurse formerly repeatedly negative to tuberculin became infected during the past few months, and showed definite progression of a subclavicular lesion during a month's observation. Because of the experience with the other 3 cases in which benignity did not prevail, treatment of this lesion resulting from first infection has been instituted. The fact that only a relatively small per cent of the total infected develop progressive tuberculosis from the first infection does not justify the conclusion that first infection tuberculosis is always benign and does not require treatment.

Because of the multiple factors involved in determining the course that a tuberculous pathologic process will take, be it either from a first or reinfection, it may be questioned whether there is sufficient justification in stating which produced the lesion, a first infection or reinfection.

Tuberculin Retests. Students failing to react to the tuberculin test on entrance to the University are requested to report for a retest each year. Of a total of 1806 retested in January, 1937, 1610 (89%) reported for a reading of their arms. Of this number, 83 (5.2%) were positive. The 196 who failed to report for interpretation of their test were probably negative, for students by receiving a yearly test soon learn to interpret a negative result, and knowing its meaning neglect to report. This would lower the rate of infection per year to 4.6%. A more complete statistical compilation of the results of retesting done in January, 1938, is indicated in Table 2. Of 2023 retested, 1829 (90%) reported for interpretation of their test. Assuming again that the 194 who failed to report had negative tests, the rate increase of infection per year would be 4.1%.

TABLE 2.—ANNUAL MANTOUX RETESTS, JANUARY, 1938.

Year enrolled.	Summoned.	Reported.		Men.					Women.					Men and women.		
				Summoned	Reported.		Pos.		Summoned	Reported.		Pos.		Tested.	Pos.	
		No.	%		No.	%	No.	%		No.	%	No.	%		No.	%
1933	264	108	41.0	248	94	37.9	6	6.4	16	14	87.5	1	7.1	108	7	6.5
1934	735	289	39.3	532	211	39.7	9	4.3	203	78	38.4	3	3.8	289	12	4.1
1935	1305	585	44.1	877	425	48.4	31	7.3	428	160	37.4	2	1.3	585	33	5.6
1936	1792	847	47.2	1153	554	48.0	23	4.2	639	293	45.9	7	2.4	847	30	3.5
Total	4096	1829*	44.6	2810	1284	45.7	69	5.3	1286	545	42.4	13	2.4	1829*	82	4.5

* A total of 2023 were tested, of which number 1829 (90%) reported for reading of test.

Since individuals showing erythema and edema measuring less than 5 mm. and who are considered negative at the time of enrollment, may in fact be infected[3] and show a 1 or 2 + reaction when retested, it is probable that the figures of 1937 and 1938 of 4.6 and 4.1% respectively represent a figure slightly higher than the actual rate of increase of infection. Of special interest is the fact that rate of increase of infection among women is only 2.4% as compared to 5.3% among men. This is consistent with the lower infection rate noted in women in all age periods. The 10-year age period 17 to 26 inclusive in which the largest number were tested, showed that of 9326 men tested 27.8% were positive, while of 4874 women tested 22.4% were positive. The differences in habits of the opposite sexes (wider social contacts of male) probably accounts for the higher rate in the male.

Roentgen Ray Study. Students having positive tuberculin tests on entering the University and those who subsequently become positive to the yearly retest receive a single postero-anterior roentgenogram of the chest. Those showing no evidence of past lesions on the Roentgen ray are reëxamined at 12 to 18-month intervals

by means of the fluoroscope. In trained hands the fluoroscope is an economical and efficient means of discovering tuberculosis. Where an infiltration or suspicion of an infiltration exists, roentgenograms of the lungs are requested. In individuals of average build, there is little difficulty in making the lesion visible. Because the patient's position is constantly being changed during the fluoroscopic examination, lesions lying well out in the periphery or obscured by the upper vertebral trunks, heart or diaphragm are brought into view. Better subsequent study by film is possible, because the examiner can request that a film be taken in the position in which it can best be seen. A small lesion may occasionally be obscured by the clavicle, or some other portion of the bony framework which on fluoroscopy, because of frequent position change, is easily enough brought into view. Additional advantages lie in viewing the excursion of the ribs, diaphragm and the mediastinum in both the lateral and oblique positions. Such routine study is not economically justifiable with films.

Differentiation between calcified deposits and blood-vessels outside the hila is readily possible by fluoroscopy. To date, individuals with calcified lesions have been reëxamined more frequently than those without such deposits, but the necessity of such procedure should be questioned. Our experience indicates that parenchymal lesions developing while in college occur in greater numbers among those without calcification. Of the 71 cases of pathologically active pulmonary tuberculosis during the 5-year period, only 12 (16%) showed evidence of calcium in the lungs or hila. In only 8 was the calcification separate and distinct from the parenchymal lesion. It would appear, therefore, that more frequent examinations are indicated among the infected showing no calcification than among those who do. Possibly in the future we may find that the ability to calcify is an index of tissue resistance.

The roentgenogram examination of 4216 students who were found to be infected by the Mantoux test is presented in Table 3. It will be noted that the classification is divided into 3 groups, namely, no Roentgen ray evidence of pulmonary tuberculosis, calcified tuberculosis and non-calcified parenchymal tuberculosis. No attempt is made to indicate whether the lesion is a primary (childhood type) or reinfection (adult type) tuberculosis.

Without the knowledge that the individual was formerly always negative to a properly administered Mantoux test to a dose of 0.005 mg. P. P. D., or its equivalent of O. T., the contention is held that one cannot with any degree of accuracy tell from the Roentgen ray film alone whether the lesion visible resulted from a first infection or reinfection. Clinical observation supports this contention. Of a group of 15 girls[6b] living in a rooming house with a sputum positive case for a period of 5 months, there were 11 who were known to have been negative to 0.005 mg. P. P. D. immediately previous to

exposure. All excepting one became infected. Two of these girls, recently infected, developed within 8 months of their exposure, subclavicular parenchymal lesions, typically so-called adult in type, which were undoubtedly progressive lesions resulting from their first infection. In another instance, a student having a positive tuberculin test was found to have a soft parenchymal lesion in the right second anterior interspace. Undoubtedly, by our present standards the lesions would have been classified as adult tuberculosis. Viewing the lesion 3 years later, marked contraction with calcification had occurred. The examiner not knowing the films were those of the same patient might now call the lesion a primary or childhood type. Recently (May,1938) 2 girls, 1 a student nurse, both negative to 0.005 mg. P. P. D. in January, 1938, and on 2 previous occasions, developed pulmonary tuberculosis. In the student nurse a soft right subclavicular infiltration 1 cm. in diameter was found by routine fluoroscopic examination done on all student nurses at 6-month intervals. The other student, an employee in a hospital, complained of chest pain and was found to have a pleural effusion. Her tuberculin test, negative in September, 1936, and in January, 1938, was now strongly positive. The lesions in both girls are undoubtedly progressive processes resulting from their first infection contracted in the preceding weeks. From the evidence unfolding itself in the study of early tuberculosis, it appears that without proof of when infection has occurred, distinction as to whether a lesion resulted from a first or reinfection is not possible or justifiable and should not be attempted.

It will be noted in Table 3 that the percentage of negative films, calcified tuberculosis and parenchymal tuberculosis is expressed for both the infected and the entire student body (the latter group includes the infected). The fact is appreciated that some of the non-reactors to tuberculin are in fact infected, and a certain number would show, if Roentgen-rayed, lesions of healed and usually calcified tuberculosis (footnote p. 519). This number, however, is small; and in no instance to date has an active case of tuberculosis been found among those failing to react to 0.005 mg. P. P. D. The necessity of reëxamination is emphasized by the fact that more cases of tuberculosis were proven active or developed subsequent to admission than were found at the time of enrollment, the ratio being approximately 3 to 2. The frequency with which infiltrations develop in lungs formerly normal by Roentgen ray emphasizes the importance of repeated examination. Of interest and significance is the fact that although the total incidence of tuberculosis among women enrolled is very slightly less (because of a lower infection rate), the incidence of active tuberculosis among the infected women is more than among the infected men—1.80% to 1.63%.

Table 4 represents roentgenogram studies by years. Because new cases are constantly developing, repeated revisions of the figures

are necessary. The group enrolling in the most recent school year shows the smallest per cent of active cases, but as new cases will be found during the coming years the number of active cases will probably approach the per cent of the preceding groups.

TABLE 3.—ROENTGENOLOGIC EXAMINATIONS.

Total Men and Women.

September, 1933, through February, 1938.

Total number positive Mantoux tests using Old Tuberculin and Purified Protein Derivative . .	4447		
Number receiving roentgenologic examination	4216		
Per cent of positive reactors receiving roentgenograms	94.8%		
Number with no Roentgen ray evidence of pulmonary tuberculosis	3003	71.3	91.0 (14,665)†
Number with calcified lesions	1022	24.2	6.3
Number with non-calcified parenchymal lesions	191	4.5	1.2
Number of positives not receiving roentgenograms—231			1.4
	4216	100.0	100.0
Number of active lesions found active on enrollment	29	0.69	0.18
Number of lesions proven active or developing subsequent to enrollment . . .	42	0.99	0.26
	71	1.68	0.44

	Percentage of those receiving roentgenograms.	Percentage of total number of students receiving tuberculin test which numbered 16,109.*

* These figures are determined by assuming that all negative reactors would show no tuberculous lesion on Roentgen ray.

† This figure is determined by subtracting total number of positives from total tested and adding the number with no Roentgen ray evidence of tuberculosis.

TABLE 4.—ROENTGENOGRAM STUDY BY YEARS.

School year.	Roentgen-ray exams.	Negative films.		Calcified lesions.		Parenchymal lesions.		Pathologically active parenchymal lesions.	
		No.	%	No.	%	No.	%	No.	%
1933 . .	529	374	70.7	128	24.2	14	2.6	13	2.5
1934 . .	751	518	70.0	189	25.2	32	4.2	12	1.6
1935 . .	953	676	70.9	240	25.2	22	2.3	15	1.6
1936 . .	1091	760	69.7	281	25.8	29	2.7	21	1.9
1937 . .	892	675	75.8	184	20.6	23	2.5	10	1.1
Total . .	4216	3003	71.22	1022	24.24	120	2.84	71	1.68

TABLE 5.—TIME OF OCCURRENCE OF ACTIVE LESIONS.

Year.	Pathologically active lesions, Number and per cent of total infected.			
	Determined on enrollment.		Determined subsequent to enrollment.	
1933	4	0.8	9	1.7
1934	6	0.8	6	0.8
1935	6	0.6	9	0.9
1936	6	0.5	15	1.4
1937	7	0.8	3	0.3
Total	29	0.69	42	0.99

The necessity of repeated examination of all the infected by fluoroscopy, films and laboratory means is indicated in Table 5. A larger number of active cases have, as previously stated, been found subsequent to rather than at the time of enrollment. There are two

reasons. The status of minimal and sub-minimal infiltrations frequently cannot be determined by one examination, and repeated study by films and laboratory methods are necessary before proof is established that the pathologic process is active and necessitates treatment. Second, infiltrations develop among the infected whose lungs appeared normal when first examined. It would appear, therefore, that a tuberculosis program to accomplish its purpose of finding the early process must not be content with one examination done at the time of enrollment, for this offers little assurance that the group will subsequently be free of disease.

Status of Lesions Found. During the 5-year period a total of 71 or a yearly average of 14.1 active cases of pulmonary tuberculosis was found. This compares to an average number of 4 in the 14-year period from 1919 to 1933, an increase of 340%. If students enrolling prior to 1933 and subsequently discovered with tuberculosis were included, the percentage increase of cases found would be well over 400%.[6a] This higher percentage of active cases can be largely explained by methods used in determining the status of the lesions found by roentgenologic examination. Because a very large percentage of the cases, especially those developing while the patient is in college, are in the minimal stage there is no clinical picture of tuberculosis. The individual with minimal or sub-minimal tuberculosis usually has no elevation of temperature, increase of pulse rate, physical signs or symptoms, though by laboratory examination there can be no doubt that the lesion is pathologically active. This determination of the status of the lesion is frequently possible before the roentgenogram shows any change either by retrogression or extension. Obviously, there is serious objection in waiting for the Roentgen ray film to show change before deciding whether the patient needs treatment. Progression as shown by the Roentgen ray film indicates further lung destruction with its longer period of treatment and less favorable prognosis. Fortunately, however, certain laboratory procedures are of special value in determining the status of early lesions. Repeated examination of the morning fasting gastric contents for tubercle bacilli by the staining of the centrifuged specimen and guinea pig inoculation usually indicates whether a lesion is active; aspirations are done on 3 successive mornings. The results obtained in 70 cases are presented in Table 6. Of interest is the group of 50 minimal cases in which the sputum (usually saliva) presented for examination was negative in every instance. Examination by stain of the centrifuged gastric contents showed 18% to be positive, while 72% of the minimal cases and 80% of the entire group were positive by guinea pig inoculation. The circumstance of 3 cases of pleurisy with effusion* in which tubercle bacilli were found in the gastric contents was not antici-

* The gastric contents in the fourth case of pleural effusion studied has recently been found positive

pated. In each instance the pleural fluid itself on diagnostic tap and guinea pig inoculation was negative, but in each case one or more of 3 guinea pigs inoculated with the gastric contents obtained on 3 successive mornings were positive. The presence of free tubercle bacilli in the lungs of cases of pleurisy with effusion is consistent with the frequent subsequent development of Roentgen ray visible pulmonary tuberculosis. Further study of the gastric contents in cases of pleurisy with effusion is obviously indicated.

TABLE 6.—EXAMINATION FOR TUBERCLE BACILLI.
(Sputum vs. Gastric Contents.)

		Sputum +.		Gastric contents. Stain +.		Pig +.	
Lesion.		No.	%.	No.	%.	No.	%.
Minimal	50	0	0	9	18.0	36	72.0
Mod. advanced	14	4	28.5	6	42.8	14	100.0
Far advanced	1	0	0	0	0	1	100.0
Miliary	1	0	0	0	0	1	100.0
Pleural effusion	3	0	0	0	0	3	100.0
Hilum tuberculosis	1	0	0	0	0	1	100.0
Total	70	4	5.7	15	21.4	56	80.0

The presence of tubercle bacilli in the gastric contents not only proves the diagnosis, but indicates that the lesion has not healed. In 3 instances lesions 1 to 2 cm. in size have revealed the presence of tubercle bacilli by guinea pig inoculation. The procedure is furthermore a good guide in determining when treatment may safely be terminated. Commonly, especially in early cases, because there have been no symptoms or fever, and because of apparent splendid clinical progress, the patient is given unwarranted permission to return to his former activities. On 4 occasions students have returned to school with permission from sanatorium physicians, because of very apparent improvement. Study of the gastric contents, however, revealed the presence of tubercle bacilli, and in each instance subsequent extension of the process occurred. Strict adherence to the principle that tuberculous lesions of the lung should not be considered healed until tubercle bacilli are repeatedly absent in the gastric contents, would result in fewer recurrences in the many patients with apparent but not real cures.

Repeated observation of the total and differential white blood cell count has been done in a number of minimal cases for a period of months. A report of the results is not possible in this review. From observations to date, it appears that when the lymphocyte count approaches or is consistently above 30% the prognosis is favorable and the process will be found to be healing.

The erythrocyte sedimentation rate in minimal cases is frequently normal and, therefore, of little value in determining pathologic activity in the early lesion. However, an increase in the rate

usually indicates a progression of the process and this usually precedes the development of symptoms.

The Active Cases. Space does not permit presentation of a complete statistical compilation of the 71 active cases found during the 5-year period. A summary is, therefore, being given. The average age of the 23 women was 23.2 years, that of 48 men was 21.6 years, making an average age of 22.1 years for the 71 cases; 27 of these, (38%), were aware of the probable source of infection. In 4 students, evidence of a tuberculous infiltration was discernible by roentgenogram within 9 months after the Mantoux test became positive.

The site of occurrence in 40 cases was unilateral, of which 22 were in the right and 18 in the left lung. Of the 5 cases of pleural effusion 3 occurred at the right base and 2 at the left. Twenty-six of the lesions were bilateral.

Of special interest is the fact that though approximately 25% of the infected (Table 3) showed calcified lesions in the lungs or hilum glands, only 16% of the active parenchymal lesions occurred in those showing calcification. The expected number of parenchymal lesions among those showing calcified deposits was 18. The actual number was 12. Further observation may indicate that the presence of calcified lesions may be interpreted as evidence of resistance against subsequent infection.

The gastric contents were examined for tubercle bacilli in 48 individuals in this group. In 43 (89.6%) the result was positive. The expectoration submitted for examination was positive in only 10 of 69 individuals, or 14.5% of the cases.

The erythrocyte sedimentation rate was increased in 33 (47.8%) of the 69 active cases receiving the test. In the early stages of the tuberculous process the test is a less accurate indicator of the status of the lesion than are examinations of the gastric contents and the repeated studies of the differential blood.

The Mantoux test was negative, as previously indicated, in 16 (22.5%), to the smaller dose of tuberculin. The necessity for the 2-dose method or less desirable single strong dose method is obvious, if all the active cases of tuberculosis are to be found.

Pleurisy with effusion was present or had occurred in 10 (14%) of the 71 cases. Students with active tuberculosis from out of state or foreign countries numbered 15 (21%). Approximately 19% of 16,109 students studied were from states other than Wisconsin.

Mention should be made of 2 cases in the series.

Case 1.—A male student, aged 22, had miliary tuberculosis involving the lungs, kidneys, prostate, epididymi and testicles, and on no occasion had constitutional symptoms. After surgical removal of the epididymi and one testicle, the patient spent 18 months in a sanatorium and is now again attending the University. By clinical and laboratory study he is free of all evidence of active tuberculosis.

Case 2.—A male student, aged 19, developed pleurisy with effusion in April, 1937. No tubercle bacilli were found in his pleural fluid, but his

gastric contents were positive. After 3 months of bed rest followed by 3 months in which he gradually increased his activity, he returned to college in the fall of 1937. His weight had increased by 20 pounds since April. According to every external physical standard he was healthy. Roentgen ray, however, now showed enlargement of the hilum glands, and gastric aspirations were found positive by guinea pig inoculation. Gastric aspirations were repeated in December, 1937, and April, 1938, and were again positive. No parenchymal lesion is visible on the Roentgen ray films. The enlargement of the hilum lymph glands persists. In this case, the total white count taken at weekly intervals has been normal, and the lymphocyte has been consistently over 30%. The blood sedimentation rate was not increased. This case suggests that though some individuals may show no Roentgen ray evidence of parenchymal tuberculosis, they may have active tuberculosis and may be definitely infectious to others.

To date a favorable course has been the rule in the large majority receiving treatment. A yearly questionnaire is sent to each student having active tuberculosis. Up to the present time no one in the group has succumbed to his disease.

The stage at which the disease was discovered is presented in Table 7. The percentage of minimal cases found at the time of enrollment (41.4%) compares favorably with the 13% for the country as a whole. Highly encouraging is the number of minimal cases (73.8%) found by examinations subsequent to enrollment. Excluding the cases of pleurisy with effusion the number found in the minimal stage approaches 84%. Unfortunately, methods making possible early discovery in a very high percentage of cases are limited to a relatively small number of the total population.

TABLE 7.—STAGE OF DISEASE (ACTIVE CASES).

	Discovered on enrollment.		Discovered subsequent to enrollment.	
	No.	%	No.	%
Minimal	12	41.4	31	73.8
Moderately advanced	13	44.9	5	11.9
Far advanced	4	13.7	0	
Miliary	0	..	1	2.4
Pleurisy with effusion	0	..	5	11.9
Total	29	100.0	42	100.0

Summary. 1. The results of a 5-year tuberculosis program among students of a mid-western university are reviewed. The importance of discovery of early pathologic processes before symptoms have occurred is emphasized.

2. A higher rate of tuberculous infection was found among the men (29.5%) than women (24.1%). Though the rate of infection was lower in the women, the incidence of active disease among the infected was higher in the female. Study of 2944 infected men for a period of from 1 to 5 years showed that 1.63% had active pulmonary tuberculosis. Study of 1272 infected females gave an incidence of 1.8%.

3. The necessity of using tuberculin for testing to a strength of

0.005 mg. P. P. D. is indicated by the fact that 16 cases or 22.5% of cases of active tuberculosis, failed to react or gave an equivocal reaction to 0.00002 mg. P. P. D.

4. A geographic variation in the incidence of infection was found. The incidence was lowest in the North Central (25.7% of students from that region) and Mountain States (26.3%). It was highest in the Desert States (84.6%), foreign countries (67.6%), Eastern States (42.8%) and Southern States (42.4%).

5. Study of infection rates by Wisconsin counties suggests a possible correlation between the death rate and incidence of infection. Of the 14 counties having the highest tuberculosis death rate, 10 are in the most northern part of the state. No other combination of 10 counties in the state gives such a high infection rate as among students from these counties.

6. Tuberculosis is classified by describing the lesions found. The contention is held that without knowledge of when infection occurred, it becomes impossible to tell by the appearance of a lesion whether it resulted from a first infection or reinfection.

7. The tuberculous lesion resulting from the first infection is not always benign. Progressive tuberculosis has developed from known first infection.

8. The determination of the status of minimal lesions found by Roentgen ray can usually be determined by laboratory methods. The gastric contents were found positive for tubercle bacilli in 72% of 50 minimal cases by stain and guinea pig inoculation. Repeated study of the total and differential blood count may indicate the probable course of the disease before changes are noted by roentgenogram. The erythrocyte sedimentation rate usually shows an increase before symptoms develop.

9. By repeated examination of the infected at regular intervals by film and fluoroscopy, 84% of the active cases of tuberculosis (excluding pleural effusions) developing subsequent to enrollment were found in the minimal stage. Only 3 students have reported to the student clinic in the past 5 years because of symptoms (excluding pleural effusions) resulting from pulmonary tuberculosis.

10. Pleurisy with effusion was present or had occurred in 14% of the active cases.

11. Treatment of minimal tuberculosis usually results in complete healing of the lesion.

Conclusion. At present, most of society's effort in combating tuberculosis is expended in caring for patients with far advanced lesions, and death or severe physical handicap is the end result. Little of the effort is directed toward the more profitable project of determining early pathologic processes before symptoms are evident and when treatment gives a complete cure.

Until all the infected as determined by the Mantoux tuberculin test receive Roentgen ray examination at regular intervals, diag-

nosis late in the disease will continue to be the rule. Methods are available to find and establish the status of the early developing lesion. In the proper direction of our efforts lies the solution of the tuberculosis problem.

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STUDIES IN DIABETES MELLITUS.

VII. NON-DIABETIC GLYCOSURIA.*

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The study here reported is concerned with 2,065 patients who, in the 35 years between 1900 and 1935, consulted Dr. Elliott P. Joslin and associates because of glycosuria which at the time of the original observation was thought not to be diabetic. These 2,065 patients comprise 14.8% of a total of 14,000 patients who came, during this same period†, for diagnosis or treatment of supposed diabetes. They were, in large part, referred by their family physicians because of glycosuria of significant degree found at multiple, rather than single examinations. Although symptoms suggesting diabetes were often absent, other abnormal conditions were not infrequently present. This was true particularly of hospital cases seen in consultation.

The aim of this study has been to determine how many of these patients subsequently became diabetic and to identify the factors which seemed to favor the development of the disease. In the

* Presented in preliminary form at the annual meeting of the Medical Section of the American Life Convention at Colorado Springs, June 17, 1937.

† Case 1 was seen in 1897 by Dr. E. P. Joslin. The first case of non-diabetic glycosuria, so listed, came in 1900.

course of the analysis, several other matters have been considered: for example, the mortality and causes of death of these cases. The patients were traced to May 1, 1937, or later, and their status as of the time of tracing has been used. Facts were sought regarding the present conditions of the patients, including results of recent tests for sugar in the blood and urine. In deceased patients, the recorded cause of death was ascertained and every effort was made to determine as carefully as possible whether the patient was considered to have had true diabetes, and if so, the basis for the diagnosis. By letter, telephone, telegraph or personal contact, *all but 32* (*1.5%*) of the 2,065 patients were traced.

Diagnostic Methods and Standards. In this clinic the standards used for diagnosis have been reasonably uniform, particularly beginning with 1920, at which time the routine examination of the blood for its sugar content came into general use. In the summer of 1926 the records of all cases of diabetes or supposed diabetes, seen up to that time, constituting approximately 5,400 of the 14,000, were carefully scrutinized and recorded diagnoses reconsidered. In cases lacking a definite diagnosis, this was supplied after a study of data obtained from the patients' records and from information received in that year as the result of a tracing during which contact was made in one way or another with almost every patient or his family physician. It is only fair to admit that in making the classifications in 1926 it was possible to use hindsight in addition to foresight and consequently a few cases then were reclassified as diabetic as of first visit. The results on these earlier cases have been to some extent biased thereby.

Four major diagnoses have been made according to the standards listed below.

The diagnosis of *diabetes mellitus* has been made when a patient with glycosuria has been found to have a fasting blood sugar (venous) of 0.14% or above or a postprandial blood sugar of 0.17% or above. These standards may with justification be criticized on two grounds: It is possible that the value of 0.14 is too high and that one of 0.13% is high enough to be considered diagnostic. Furthermore, and we think with more justification, in some cases, particularly those in which the diagnosis is made on the basis of a glucose tolerance curve, the postcibal value of 0.17% may be regarded by some as too low. However, over a period of years these standards have worked very well and we have continued to use them for the sake of uniformity. When using capillary blood, we have required that the postprandial blood sugar be 0.20% or above in order to make the diagnosis of diabetes and experience suggests that even this is not allowing enough difference between venous and capillary values. Thus in one case (13368) at two different intervals of time following the giving of glucose, the capillary-venous difference amounted to 0.08%.

Folin's[2-4] methods of analysis have been used throughout.

The diagnosis of *potential diabetes* is not often made and its criteria are not rigid or well-defined. We have at times discussed discontinuing such a classification but upon each occasion valid reasons persuaded us to retain it. In general, it has represented a clinical impression and has been reserved for those cases with a fasting blood sugar of 0.12 or 0.13%, a postprandial value of 0.15 or 0.16% and glycosuria dependent upon diet, particularly if the patient has a history of diabetes in the family.

Renal glycosuria in the limited sense in which we have used it denotes constant glycosuria even in the fasting state, fasting blood sugar values below 0.12%, postprandial values below 0.17% and an absence of diabetic symptomatology. The typical sugar tolerance curve is, however, almost flat, with a normal initial value. Patients with renal glycosuria in this series are, therefore, individuals whose renal threshold for sugar is extremely low, usually corresponding to a blood sugar of 0.10% or lower. In previous articles on renal glycosuria[6a,b] considerable emphasis has been placed upon a time element essential for the diagnosis and an arbitrarily chosen period of 3 years has been established as necessary. However, excluding cases of temporarily marked lowering of the renal threshold as seen notably in pregnancy, the necessity of such a time interval is doubtful. If one finds glycosuria constantly even in the fasting state in a patient without diabetic symptomatology and if during a glucose tolerance test an unequivocably normal response is obtained, the chances are overwhelming that one is dealing with renal glycosuria. Caution must be advised against accepting as normal, tolerance curves which either at the highest point or subsequent fall are on the borderline of the type found in mild diabetes. Patients showing such curves should be kept under close observation and reëxamined at suitable intervals before making a definite diagnosis.

It is evident from the above that many transient or intermittent glycosurias often referred to as "renal glycosuria" are excluded from such a classification in this paper.

Although the cases of glycosuria of pregnancy usually represent instances of a lowering of the renal threshold for sugar, the condition is transient, lasting only for the duration of the pregnancy. This characteristic sets this group sharply apart from that in which there is a permanently lowered renal threshold.

The "*unclassified*" *glycosuria* group is the residual class into which all other cases of glycosuria are placed. This group includes cases of alimentary glycosuria, those with a renal threshold for sugar slightly below the average, also patients with infections or toxemias, with chronic or degenerative conditions, with hyperthyroidism and hyperpituitarism, and with various other conditions, which may at times cause glycosuria which is usually temporary and slight. In many of these patients, despite the history of glycosuria, no urinary sugar was found during the period of initial observation.

Under the heading of "*deferred diagnosis*" have been placed those patients, most of them recently seen, for whom, up to the time of the present study, available data were inadequate for proper diagnosis.

In establishing the diagnosis in any individual case the following procedure has been employed: Random urine and blood specimens are obtained at the patient's first visit regardless of the time of day. If the values for the blood sugar are below those accepted as indicating diabetes, the patient may be requested to return for similar tests at 45 to 60 minutes after an ordinary mixed meal liberal in carbohydrate. In an attempt to establish the diagnosis at the initial visit, particularly in patients who may not be seen again, 50 gm. of glucose may be given orally at this time and blood and urine tests made 45 to 60 minutes later.

If these convenient diagnostic steps do not enable one to make a diagnosis, then recourse is had to a formal sugar tolerance test. At present and for the most part, we have used 100 gm. of glucose as the test load for adult patients, although for a few years prior to January 1, 1935, at Professor Folin's suggestion, we used 75 gm. of sucrose. Starting with the patient in the fasting state or 5 hours after a meal, samples of urine and venous blood are taken before the giving of sugar and at $\frac{1}{2}$, 1, 2 and occasionally 3 hours afterward. Interpretation is based both upon the height and the subsequent rate of fall of the curve obtained.

The authors and their associates freely concede the difficulties which are occasionally encountered by close adherence to rigid diagnostic standards such as those outlined above. The chief error, if such there be, arises in the classification of a glycosuric patient as a diabetic simply because a venous blood sugar value of 0.17% is obtained. However, one must have definite standards of diagnosis and abide by them, since otherwise confusion is inevitable. One cannot rely on clinical symptoms because of the well-known absence of such in certain stages of the disease in patients with undoubted diabetes. Fortunately, those situations in which diagnosis is difficult are not common enough to change the outcome of this analysis. Parenthetically, it should be stated that in the actual treatment of the patient, conclusions from laboratory data are modified by clinical judgment.

Description of Material. The 2,065 patients mentioned at the beginning of the paper include (*a*) 38 patients who, after further study within 3 months of the time of the initial visit, were diagnosed as diabetic ("*reconsidered*" diagnosis), or on whom subsequent review of the data of original examination showed an error in the diagnosis and who, therefore, were diabetic from the start ("*rejected*" change of diagnosis); (*b*) 81 patients classed as "*deferred*" on whom the data did not permit a definite diagnosis. If these 119 cases are excluded, the number of non-diabetics was 1,946, or 13.9% of the original group of 14,000 patients.

These 1,946 cases which exclude the *rejected*, *reconsidered* and *deferred* diagnoses, form the actual basis of the present study. Of this total, 1,142 were males and 804 females, divided according to age as shown in Table 1.

With regard to the date of initial observation, 197 came first to the clinic prior to 1920, 1,097 in the decade 1920 to 1929, and 652 between 1930 and October, 1935.

TABLE 1.—SEX AND AGE DISTRIBUTION OF PATIENTS WITH NON-DIABETIC GLYCOSURIA. EXPERIENCE OF E. P. JOSLIN AND ASSOCIATES, BOSTON, MASS., 1900–1937.

Age at first visit.	Total.	Males.	Females.
All ages	1946	1142	804
Under 20	363	215	148
20 to 39	648	337	311
40 to 59	688	443	245
60 and over	247	147	100
Average age	37.7 years		

Medical examination for life insurance was the basis of the history of glycosuria in 285, or 14.6% of the group. The proportion of such cases varies widely by sex and age, in accordance with the typical make-up of the group of persons applying for insurance requiring such examination. Thus, 23.1% of the males and only 2.6% of the females were referred because of glycosuria discovered at examination for insurance. The percentages were nominal among males under 20 and over 60, but between those ages, over 30% came because of the findings at an insurance examination.

Incidence of Various Types of Non-diabetic Glycosuria. Table 2 shows the number and percentage of cases in each classification. The original diagnoses are given for all 2,065 patients, including the 38 *rejected* or *reconsidered* and the 81 *deferred* diagnoses, and the final diagnoses for the 1,946 considered to fall within the scope of this paper. The authors have felt that these excluded cases should be mentioned, but should not enter into the subsequent analysis.

Potential diabetes was the diagnosis in 12.0% of the total cases, and 12.3% of the definitely non-diabetic group. *Renal glycosuria* accounted for 3.2% of the original diagnoses, but only 2.3% of the final non-diabetic classification. *Deferred* diagnoses accounted for 3.9% of the total. By far the largest group, containing more than 80% of the cases, consisted of those with *unclassified* glycosuria.

Changes of Diagnoses Within the Non-diabetic Classification. These internal changes are relatively few but have special significance. The originally rather loose concept of renal glycosuria has been modified in this clinic in late years to include only those cases with an extremely low renal threshold for sugar; such rigid requirements have reduced the number of cases. In the judgment of the associ-

ates of the George F. Baker Clinic, no patient with true renal glycosuria has progressed to diabetes. The records of the 3 patients

TABLE 2.—ORIGINAL AND FINAL CLASSIFICATIONS OF PATIENTS WITH NON-DIABETIC GLYCOSURIA. EXPERIENCE OF E. P. JOSLIN AND ASSOCIATES, 1900–1937.

Classification.	Original classification.		Final classification excluding reconsidered, rejected and deferred diagnoses.*	
	Number.	Per cent.	Number.	Per cent.
Total	2065	100.0	1946	100.0
Potential diabetes	247	12.0	240	12.3
Renal glycosuria	67	3.2	45	2.3
Glycosuria of pregnancy	8	0.4	9	0.5
Pentosuria	3	0.1	3	0.2
Levulosuria	1	..	1	0.1
Diabetes mellitus	1	..	..	..
Diabetes insipidus	1	..	1	0.1
Unclassified	1656	80.2	1647	84.6
Deferred	81†	3.9	..	..

* The changes in the excluded cases are as follows:
Of 25 rejected changes (cases now considered diabetic from the beginning), 8 were originally diagnosed as potential diabetics, 2 as renal glycosurics and 15 as unclassified.
Of 13 reconsidered (cases for whom additional data within 3 months proved the patients diabetic), 3 were originally diagnosed as potential diabetics and 10 as unclassified.

† Includes 1 case definitely proved pentosuric early in 1938.

in whom the diagnosis of renal glycosuria was made originally and at a later date changed to diabetes, have been carefully studied. In each case the original diagnosis of renal glycosuria has been discarded as unwarranted by the data available. Even more cases originally classified as renal glycosuria have been rediagnosed as unclassified glycosuria because they did not conform to the diagnostic criteria previously stated. Subsequent review of the original records at various times or subsequent observations of patients have caused changes in the diagnosis of a few other cases from one non-diabetic classification to another. The total number of changes within the non-diabetic classification was 34. The frequency of each type of change is shown in the following table.

CHANGES FROM ONE NON-DIABETIC CLASSIFICATION TO ANOTHER.

From.	To.	Number of cases.
Renal glycosuria	Potential diabetes	1
Renal glycosuria	Unclassified	23
Potential diabetes	Renal glycosuria	1
Potential diabetes	Glycosuria of pregnancy	1
Unclassified glycosuria	Renal glycosuria	2
Unclassified glycosuria	Potential diabetes	5
Diabetes mellitus	Renal glycosuria	1

Subsequent Incidence of Diabetes. Of the 1,946 patients forming the basis of this study, in 193 (9.9%) subsequent findings up to the

date of tracing in 1937 have warranted the assumption that true diabetes mellitus has developed. The subsequent incidence of diabetes according to the final non-diabetic classifications was 40 (16.7%) of the *potential* diabetics; one (11.1%) of the patients with *glycosuria of pregnancy*; and 152 (9.2%) of the *unclassified* cases. As already stated, no case of renal glycosuria (in the limited sense used in this Clinic) has developed diabetes. This fact is emphasized to bring out the lack of relationship between the two conditions. In our opinion, renal glycosuria is not a true disease but simply a striking deviation from the average normal as regards the renal threshold for sugar. Patients with diabetes may also have renal glycosuria. It seems reasonable that if one could follow for a period of years a sufficiently large group of individuals with a very low renal threshold for sugar, some of them, possessing certain favoring influences such as obesity and the presence of diabetes in relatives, would develop diabetes mellitus just as do persons in the general population with an average normal threshold. Such development of diabetes would not necessarily, however, signify any connection between the two conditions.

As we have previously indicated, all but a small number of the patients have been traced at least to May 1, 1937, but some were not traced until later and any diabetics discovered subsequent to May 1, 1937, have been included in the total. The following sections take up the chief factors in the onset of diabetes in these cases.

Age. As Table 3 shows, the percentage of changed diagnoses increases with advancing age in the four broad age groups distinguished. The rise is marked prior to age 60, but increases very little after that age.

TABLE 3.—AGE IN RELATION TO SUBSEQUENT INCIDENCE OF DIABETES AMONG NON-DIABETIC GLYCOSURICS. EXPERIENCE OF E. P. JOSLIN AND ASSOCIATES, 1900–1937.

Age at examination.	Subsequent diabetes.	
	Number.	Per cent.
All ages	193	9.9
Under 20	9	2.5
20–39	39	6.0
40–59	104	15.1
60 and over	41	16.6

Sex. No significant difference by sex in the subsequent incidence of diabetes was found (see Table 4). The data are given by age. They show that this negative finding according to sex is not a result of age differences between the two sexes. On the basis of this result, therefore, no subsequent distinction by sex has been made.

Weight. The percentage of cases developing diabetes increases distinctly with weight. This phase of the study has been made both from the point of view of the weight found at the initial examination and on the basis of the previous maximum weight. The patients have been classified at both dates according to the percentage departure from average weight, with allowance for sex, height and age.

TABLE 4.—SEX IN RELATION TO SUBSEQUENT INCIDENCE OF DIABETES AMONG NON-DIABETIC GLYCOSURICS. EXPERIENCE OF E. P. JOSLIN AND ASSOCIATES, 1900–1937.

Age at examination.	Subsequent diabetes.			
	Per cent.		Number.	
	Males.	Females.	Males.	Females.
All ages	10.2	9.6	116	77
Under 20	2.8	2.0	6	3
20–39	5.9	6.1	20	19
40–59	14.4	16.3	64	40
60 and over	17.7	15.0	26	15

Weight at Initial Examination. At all ages only 6.0% of those underweight at examination developed diabetes, as compared with 10.6% of those of average weight, 12.0% of those less than 20% overweight and 16.6% of those 20% or more overweight. This trend is consistent in all age groups in which there are sufficient numbers of cases to give reliable ratios.

Previous Maximum Weight. The data based upon the maximum weights before initial visit give even more clear-cut differences than do those based upon weights at the first visit. The latter have been presented first because they represent actual observations and are, therefore, more strictly accurate than the maximum figures reported by the patient. For certain uses also, such as insurance work, the data as of initial examination are more practicable because reliable data on weights previous to examination are seldom available to the physicians of life insurance companies.

At all ages, the incidence of subsequent diabetes, according to previous maximum weights, rises successively from a minimum of 3.2% among underweights to a maximum of 17.0% among those 20% or more overweight. This trend is present in all age groups except the youngest, those under 20 at original observation. The data on build at examination and at previous maximum weight are given in Table 5.

Heredity. The presence or absence of a family history* of diabetes at first glance (see Table 6) would seem to have had little or no

* Within restricted degree of relationship, viz., parents, grandparents, children, siblings, uncles and aunts, and first cousins.

influence upon the subsequent incidence of the disease in these patients with non-diabetic glycosuria. Among those with a positive

TABLE 5.—BUILD IN RELATION TO SUBSEQUENT INCIDENCE OF DIABETES MELLITUS AMONG NON-DIABETIC GLYCOSURICS. NUMBER AND PER CENT OF PATIENTS BECOMING DIABETIC IN GROUPS CLASSIFIED BY PERCENTAGE DEPARTURE FROM AVERAGE WEIGHT, FOR SEX, HEIGHT AND AGE (*a*) AT EXAMINATION AND (*b*) AT MAXIMUM WEIGHT PRIOR TO EXAMINATION. EXPERIENCE OF E. P. JOSLIN AND ASSOCIATES, 1900–1937.

Age at initial examination.	Build group.							
	Per cent becoming diabetic.				Number becoming diabetic.			
	Underweight.	Average weight.	Overweight.		Underweight.	Average weight.	Overweight.	
			5% to 19%.	20% and over.			5% to 19%.	20% and over.
Weight at initial examination								
All ages . .	6.0	10.6	12.0	16.6	38	46	46	39
Under 20 .	5.3	1.0	....	4.5	6	1	..	1
20–39 . .	3.3	6.8	9.0	10.3	8	10	10	8
40–59 . .	8.7	16.1	19.0	23.6	18	22	28	25
60 and over	8.1	27.1	18.6	17.2	6	13	8	5
Previous maximum weight								
All ages . .	3.2	4.2	11.9	17.0	7	13	55	94
Under 20 .	3.0	2.9	2.2	5.9	1	1	1	1
20–39 . .	3.0	2.3	7.5	9.2	3	3	13	16
40–59 . .	4.4	5.7	13.6	23.0	3	6	25	60
60 and over	...	8.1	26.7	16.7	..	3	16	17

TABLE 6.—HEREDITY IN RELATION TO SUBSEQUENT INCIDENCE OF DIABETES MELLITUS AMONG NON-DIABETIC GLYCOSURICS. NUMBER AND PER CENT OF PATIENTS BECOMING DIABETIC AMONG GROUPS CLASSIFIED ACCORDING TO FAMILY HISTORY OF DIABETES. EXPERIENCE OF E. P. JOSLIN AND ASSOCIATES, 1900–1937.

Age at examination.	Subsequent diabetes.			
	Per cent.		Number.	
	Positive family history.	Negative family history.	Positive family history.	Negative family history.
All ages	10.0	9.9	51	142
Under 20	4.7	0.9	7	2
20–39	7.8	5.3	14	25
40–59	16.9	14.7	24	80
60 and over	15.0	16.9	6	35

family history, the percentage at all ages combined of patients with non-diabetic glycosuria who became diabetic was 10.0%, as compared with 9.9% among those with a negative family history. The group

with a positive family history, however, is definitely younger, about 9 years on the average, than that with a negative family history, and as Table 6 shows, when the data are analyzed according to age, the percentage becoming diabetic is higher in the positive family history group than in the negative group, except at ages 60 and over. The younger the age, the greater is the difference. If the proportion of those becoming diabetic were the same at each age in the positive group as in the negative group, the number becoming diabetic in the positive heredity group would be only 39, as compared with 51 actually found. On the basis of this analysis, one may draw the conclusion tentatively that heredity is a factor in the subsequent development of diabetes in the younger patients with glycosuria.

Duration. The length of time elapsed since original observation obviously must be of importance unless all the cases of diabetes among these patients were to develop within a relatively short time after examination. This is clearly not the case. Consequently, when the incidence of diabetes is noted for groups first observed before and since 1927, much higher percentages of changed diagnoses

TABLE 7.—DURATION SINCE EXAMINATION IN RELATION TO SUBSEQUENT INCIDENCE OF DIABETES AMONG NON-DIABETIC GLYCOSURICS. COMPARISON OF PATIENTS FIRST OBSERVED PRIOR TO AND SINCE 1927. EXPERIENCE OF E. P. JOSLIN AND ASSOCIATES, 1900–1937.

Age at examination.	Subsequent diabetes.			
	Per cent.		Number.	
	First examined prior to 1927.	First examined 1927 and later.	First examined prior to 1927.	First examined 1927 and later.
All ages	14.4	6.4	124	69
Under 20	5.6	1.2	6	3
20–39	8.0	4.2	25	14
40–59	21.0	9.3	72	32
60 and over	21.2	13.5	21	20

are found in every age group among the earlier cases than among the later ones. At all ages combined, 14.4% of the earlier group of patients have become diabetic, compared with only 6.4% of the more recent group. The actual difference is probably somewhat larger, since at least a few early cases were reclassified as diabetic at first observation, when the records were reviewed in 1926, and thus do not enter this experience. On the other hand, in the earlier group, diagnostic procedures were not as well developed or standardized as since 1927; consequently, the later cases which have been more thoroughly studied are less subject to error of diagnosis. The proportions becoming diabetic in the groups first observed before and since 1927 are given in Table 7.

In the divisions of the material presented thus far, duration has not biased the results, but in the subsequent section relating to diagnostic procedures which have changed during the period covered in this study (*e. g.*, blood sugar examinations and tolerance tests), the matter is vital. In such cases the proportions of changed diagnoses *in relation to the years of life exposed* give a more accurate picture when there are differences in average duration between the groups compared. This is brought out by Table 8 which gives the proportions becoming diabetic per 1,000 years of life exposed for the same groups used in Table 7, namely, patients first coming under observation prior to 1927 and those since 1927. On this basis, the ratios, for the early and the more recent patients, are almost identical. At no point is there a really significant difference. To a certain extent, this is surprising, because the average attained age of the earlier cases is greater and one would on that account alone expect a higher proportion of subsequent diabetes among them than among the more recent cases. This result, however, probably reflects the fact that the original classification of some of these cases was made shortly before 1927 and there probably is some bias in the earlier material on that score. Reference to this matter has been made earlier.

TABLE 8.—SUBSEQUENT INCIDENCE OF DIABETES PER 1000 YEARS OF LIFE EXPOSED AMONG PATIENTS WITH NON-DIABETIC GLYCOSURIA FIRST EXAMINED PRIOR TO 1927 AND THOSE FIRST EXAMINED IN 1927 AND LATER YEARS. EXPERIENCE OF E. P. JOSLIN AND ASSOCIATES, 1900–1937.

Age at examination.	Subsequent diabetes per 1000 years of life.	
	First examined prior to 1927.	First examined 1927 and later.
All ages	11.8	11.3
Under 20	4.1	2.1
20–39	5.7	7.0
40–59	18.3	16.3
60 and over	27.5	30.1

Age, Maximum Weight, Family History and Duration Considered Simultaneously. The foregoing analysis, which has shown age and weight and duration as distinct factors favoring incidence of diabetes in non-diabetic glycosuria, heredity as a slight influence and sex as of no influence, assumed for each item that the data were unbiased as to other items, except with regard to age which has been consistently taken into account. In order to test the validity of this assumption and, therefore, of the differences found, the data have been split into smaller groups in which all these factors are taken into account. To avoid having to deal with groups that are too small to give reliable results, however, average and underweights are combined and overweights are considered as a class.

The results of this division of the material (Table 9) confirm the individual items which were found of positive influence, and bring out their relative importance. Build and age are of approximately equal influence. The former is possibly of slightly greater importance, because in very few instances is there a higher percentage of subsequent diabetes in the lighter weight group than in overweights,

TABLE 9.—INFLUENCE OF SEVERAL FACTORS CONSIDERED SIMULTANEOUSLY ON SUBSEQUENT INCIDENCE OF DIABETES MELLITUS AMONG NON-DIABETIC GLYCOSURICS. NUMBER AND PER CENT OF PATIENTS BECOMING DIABETIC IN GROUPS CLASSIFIED BY AGE AT EXAMINATION, PREVIOUS MAXIMUM WEIGHT AND PRESENCE OR ABSENCE OF DIABETES IN THE FAMILY. PATIENTS FIRST SEEN PRIOR TO AND SINCE 1927 SEPARATELY. EXPERIENCE OF E. P. JOSLIN AND ASSOCIATES, 1900–1937.

Heredity; age at examination.	Per cent becoming diabetic.				Number becoming diabetic.			
	First examined prior to 1927.		Examined 1927 or later.		First examined prior to 1927.		Examined 1927 or later.	
	Average or under-weight.	Over-weight (5% or more).	Average or under-weight.	Over-weight (5% or more).	Average or under-weight.	Over-weight (5% or more).	Average or under-weight.	Over-weight (5% or more).
Total								
All ages	4.9	21.0	3.0	9.2	11	99	9	50
Under 20	4.3	10.0	2.2	....	1	2	1	..
20–39	1.9	11.8	3.1	5.1	2	20	4	9
40–59	7.7	26.7	3.2	11.4	6	60	3	25
60 and over	11.1	29.3	2.9	15.4	2	17	1	16
Positive family history of diabetes mellitus								
All ages	4.7	21.0	4.3	7.5	2	26	4	10
Under 20	9.1	22.2	4.0	....	1	2	1	..
20–39	5.3	9.6	5.1	6.1	1	5	2	3
40–59	....	35.2	....	6.7	..	19	..	3
60 and over	....	....	14.3	23.5	..	..	1	4
Negative family history of diabetes mellitus								
All ages	5.0	21.0	2.4	9.7	9	73	5	40
Under 20	....	....	....	....	....	....	....	..
20–39	1.2	12.8	2.3	4.7	1	15	2	6
40–59	8.8	24.0	4.1	12.6	6	41	3	22
60 and over	13.3	34.7	....	13.8	2	17	..	12

whereas in a few groups of average weight or less, the increase by age is not marked or is absent. This confirms the previous observation that build is a vital factor except at ages under 20. Rather large differences were fairly consistently found by duration, but these were inevitable and were less marked than might be expected, especially when the greater attained age of the earlier cases is taken into account. The slight influence of heredity is again brought out, for there was no consistent difference between the heredity and

non-heredity groups when the other factors were simultaneously considered.

Jewish and Non-Jewish Patients Compared. The subsequent incidence of diabetes was much greater among Jewish patients originally diagnosed as non-diabetic than among non-Jewish patients. This observation holds at every age, even though the numbers in certain of the groups are rather small. In this analysis, the factor of sex has been considered and it was found that the subsequent incidence of diabetes was particularly high in females. The facts are given in Table 10.

TABLE 10.—SUBSEQUENT INCIDENCE OF DIABETES IN JEWISH AND NON-JEWISH PATIENTS WITH NON-DIABETIC GLYCOSURIA. NUMBER AND PER CENT OF PATIENTS BECOMING DIABETIC. EXPERIENCE OF E. P. JOSLIN AND ASSOCIATES, 1900–1937.

Age at examination.	Subsequent diabetes.											
	Per cent.						Number of cases.					
	Both sexes.		Males.		Females.		Both sexes.		Males.		Females.	
	Jews.	Non-Jews.	Jews.	Non-Jews.	Jews.	Non-Jews.	Jews.	Non-Jews.	Jews.	Non-Jews.	Jews.	Non-Jews.
All ages	18.5	7.9	16.8	8.6	20.9	6.9	68	125	36	80	32	45
Under 20	5.4	2.0	6.5	2.2	4.0	1.6	3	6	2	4	1	2
20–39	14.3	3.6	13.9	3.5	14.7	3.7	21	18	11	9	10	9
40–59	25.7	12.4	21.1	12.7	34.0	11.8	36	68	19	45	17	23
60 and over	33.3	14.8	28.6	16.5	40.0	12.2	8	33	4	22	4	11

Analysis of the records of Jewish patients shows that the proportion of overweights was higher than among non-Jewish patients, but even when allowance was made for that and also for duration since first observation, the incidence of diabetes was still significantly higher among the Jewish patients than among non-Jews.

Adequate Study. The care with which the patient is studied should be considered in relation to the subsequent incidence of diabetes. A group of patients termed by us the "adequate study" group has been distinguished, in which have been included those with two or more blood sugar values (at least one of them at 20 to 60 minutes after a meal) at original observation.*

Table 11 shows the subsequent incidence among the group with "adequate study" as compared with other patients. In this table the proportions becoming diabetic are presented not only as percentages but also as rates of changed diagnosis per 1,000 years of life exposed. The latter basis is the more accurate, because the procedures for more thorough study of patients have been gradually

* This period covers the first 3 months after initial observation.

introduced and therefore most of the "adequately studied" patients have been seen in comparatively recent years. The experience on patients first observed prior to and since 1927 has also been distinguished. The comparisons between the more recent patients have greater validity.

TABLE 11.—ADEQUACY OF ORIGINAL STUDY IN RELATION TO SUBSEQUENT INCIDENCE OF DIABETES IN NON-DIABETIC GLYCOSURICS. EXPERIENCE OF E. P. JOSLIN AND ASSOCIATES, 1900–1937.

Age groups; examination years.	Subsequent diabetes.											
	Per 1000 yrs. of life exposed.				Per cent				Number of cases.			
	Adequately studied*				Adequately studied*				Adequately studied*			
	Total.	Without tolerance test.	With tolerance test.†	Others.	Total.	Without tolerance test.	With tolerance test.†	Others.	Total.	Without tolerance test.	With tolerance test.†	Others.
Total.												
All ages	10.3	11.7	6.3	12.6	7.4	10.2	3.1	12.5	74	62	12	119
Under 20	3.1	4.7	....	3.0	2.1	4.0	....	2.9	4	4	..	5
20–39	7.3	8.2	4.8	5.1	5.8	8.1	2.6	6.3	22	18	4	17
40–59	15.9	18.5	7.2	18.8	11.6	15.6	3.7	18.3	38	34	4	66
60 and over	18.8	14.3	36.0	34.6	9.8	8.5	12.9	21.4	10	6	4	31
Examined 1927 and later												
All ages	10.4	12.8	7.2	13.0	5.7	8.4	3.3	7.5	41	29	12	28
Under 20	1.1	1.9	....	3.5	0.6	1.4	....	2.0	1	1	..	2
20–39	7.0	8.6	5.5	6.8	4.0	6.1	2.7	4.5	10	6	4	4
40–59	16.6	21.4	8.5	15.6	9.3	13.9	3.9	9.2	21	17	4	11
60 and over	24.7	19.7	36.0	36.8	10.6	9.3	12.9	17.5	9	5	4	11
Examined prior to 1927												
All ages	10.1	10.9	....	12.5	11.8	12.5	....	15.7	33	33	..	91
Under 20	7.7	9.4	....	2.8	9.7	11.1	....	3.9	3	3	..	3
20–39	7.5	8.0	....	4.7	9.2	9.8	....	7.1	12	12	..	13
40–59	15.1	16.3	....	19.6	16.7	17.7	....	22.8	17	17	..	55
60 and over	6.0	6.0	....	33.4	5.9	5.9	....	24.4	1	1	..	20

* At least 2 blood sugar values, one of them at 20 to 60 minutes after a meal.
† Cases with tolerance test within 3 months of first visit.

The most striking difference in the table is the markedly lower proportion of subsequent diabetes in those given a glucose tolerance test at first observation. This result probably reflects the successful diagnosis at original observation of mild diabetes in many patients who therefore are excluded from the non-diabetic series. Apart from this group, the differences between the "adequately studied" cases and the rest are slight and inconsistent. Most certainly the relatively high incidence of subsequent diabetes among the "adequately studied" cases reflects the large number of cases of difficult diagnosis in the group and not faults in the routine of study. In judging the results of the comparison of the more carefully studied cases with the others, this consideration must be kept in mind.

It must be acknowledged that the percentage becoming diabetic among those given a tolerance test, low as it is, is higher than expected. In 4 of the 12 patients in this group, the original tolerance

test was faulty in that it was carried out at 1 hour after breakfast and for this reason the results cannot be accepted as entirely valid. Experience has shown that a fast of at least 5 and preferably 12 hours is advisable before giving the sugar used as a test load. In 7 of the 12 cases sucrose was given; our experience suggests that more uniform results are obtained with glucose. In 4 of the 12 cases the original tolerance curves were difficult to interpret and were not strictly normal because, despite the fact that no blood sugar value higher than 0.16% was obtained during the tests, the 2-hour values were not absolutely normal. Case 8131, a physician and the only fatal case in the group, died at the age of 74.2 years with renal block and uremia. He had never considered that he had diabetes. Terminally he developed glycosuria and marked hyperglycemia. Case 8809 was 3 months pregnant in August, 1933, when the second tolerance test at which diabetes was diagnosed was carried out; in May, 1937, she considered herself well and was taking no insulin. Only 3 of the 12 cases have developed diabetes of a degree that insulin was or is needed and in 2 of these the original tolerance curve was not strictly normal. In 2 other cases, abnormal blood sugar values had been obtained elsewhere prior to the first visit here.

It is clear that in the majority of these 12 cases unusual circumstances existed. In 4 cases, however, there seems to have been definite progression from an unimportant to a significant impairment of carbohydrate tolerance.

Blood Sugar Level at Original Examination. The subsequent incidence of diabetes among patients thought to have non-diabetic glycosuria at first visit increases with the level of the blood sugar at the initial observation. The rate is low among those with low or normal blood sugars and is high (30.5%) among those with a blood sugar level close to that of true diabetes (0.13%). Table 12 gives the results of an analysis according to blood sugar at first examination. Three groups of blood sugar values are distinguished, namely, fasting, at 1, and at 2 or more hours after food or sugar (glucose or sucrose). There were too few observations at other intervals to permit study. Cases have been used once at each of these intervals, for which a reading appears in the record. Where two or more observations for a particular interval (*e. g.*, in the fasting state) were available for a given patient, the highest was used. The data in this table indicate the importance of subsequent tests particularly on those patients with suspicious or borderline blood sugar values. The percentages becoming diabetic rose as high as one-fourth to one-third or more of the cases in certain groups. The fasting and 2-hour values gave more distinct results than the 1-hour readings. This may, however, be purely an artefact. There are few borderline readings at 1 hour after food, possibly because a stricter diagnostic attitude was taken for those with a borderline

postprandial blood sugar. It is notable that age is a factor in this analysis also. The percentage of subsequent diabetes increases with age in most of these blood sugar groups.

TABLE 12.—BLOOD SUGAR LEVEL AT ORIGINAL EXAMINATION IN RELATION TO SUBSEQUENT INCIDENCE OF DIABETES IN NON-DIABETIC GLYCOSURICS. NUMBER AND PER CENT OF PATIENTS BECOMING DIABETIC IN GROUPS CLASSIFIED BY BLOOD SUGAR VALUES. EXPERIENCE OF E. P. JOSLIN AND ASSOCIATES, 1900–1937.

Blood sugar, per cent.	Subsequent diabetes.							
	Per cent.				Number of cases.			
	All ages.	Under 40	40–59	60 and over.	All ages.	Under 40	40–59	60 and over.
Fasting								
.08 or less	6.4	4.8	10.3	....	7	3	4	..
.09–.10	8.8	6.7	10.2	13.6	15	6	6	3
.11–.12	23.9	12.1	33.3	18.2	22	4	16	2
.13 or more*	30.5	15.0	36.7	30.8	25	3	18	4
One hour p. c.								
.12 or less	4.1	3.3	5.5	5.9	8	4	3	1
.13–.14	13.1	7.4	22.7	8.3	8	2	5	1
.15–.16	12.8	....	18.8	33.3	5	..	3	2
Two hours or more p. c.								
.08 or less	4.8	3.5	6.3	8.3	7	3	3	1
.09–.10	5.3	2.8	4.5	17.6	14	4	4	6
.11–.12	13.5	4.1	23.2	19.2	21	3	13	5
.13 or more	31.7	22.2	37.8	44.4	26	8	14	4

* The figures in this line indicating the subsequent incidence of diabetes in patients with a fasting blood sugar of "0.13% or more" must not be interpreted too strictly. Naturally the reader recalls statements earlier in this paper to the effect that a fasting blood sugar of 0.14% is considered diagnostic of diabetes and hence wonders why the cases now under discussion were not so classified at original observation. The reasons were various but chiefly: (1) lack of accompanying glycosuria; (2) lack of confirmation of diagnosis by subsequent tests of blood and urine; (3) questionable values; (4) failure to record time of day blood was drawn; (5) complicating conditions in themselves capable of producing transient slight abnormalities in the blood sugar.

Striking also are the results of the analysis in cases with readings at two or more intervals, with relation to food or glucose. This analysis is restricted to the same three intervals as the preceding section, namely, fasting, 1 hour and 2 hours or more after food. While the numbers are small, the results are definite. The proportion of patients subsequently becoming diabetic is highest when both of two readings are above average and lowest when both are normal. The results were equally significant in the groups with *fasting—1 hour*, and *fasting—2 hour or more* blood sugar readings. The comparative level of the fasting and 2 hour or more blood sugars yielded negative results.

Comparison of Probability of Becoming Diabetic for Non-diabetic Glycosurics and Unselected Population Groups. The question may

properly be raised as to whether the incidence of diabetes among patients with non-diabetic glycosuria is any higher than that for a group of persons picked at random. The answer is decidedly in the affirmative, although exact measurement cannot be made of the relative incidence of diabetes in the two groups. The incidence of diabetes in random groups may be measured by the probability

TABLE 13.—BLOOD SUGAR LEVEL AT TWO INTERVALS IN RELATION TO SUBSEQUENT INCIDENCE OF DIABETES IN NON-DIABETIC GLYCOSURICS. NUMBER AND PER CENT OF PATIENTS BECOMING DIABETIC IN GROUPS CLASSIFIED BY BLOOD SUGAR LEVELS.* EXPERIENCE OF E. P. JOSLIN AND ASSOCIATES, 1900–1937.

Blood sugar, per cent.	Subsequent diabetes.	
	Per cent.	Number of cases.
Fasting (A) and one hour (B)		
A = .11 or more *and* B = .14 or more	67	4
A = .11 or more *or* B = .14 or more	17	3
A = .10 or less *and* B = .13 or less	7	4
Fasting and two hours		
Both .11 or more	75	3
Either .11 or more	13	1
Both .10 or less	9	2
One hour (C) and two hours (D)		
C = .14 or more *and* D = .11 or more	25	1
C = .14 or more *or* D = .11 or more	13	2
C = .13 or less *and* D = .10 or less	5	2

* Where consecutive blood sugar values were available after a test meal or tolerance test, these were used, in preference to the highest values of the fasting, 1 hour and 2 hour or more specimens, taken on different occasions. When the data were available for the three intervals, the case was tabulated in all three combinations of the table.

of eventually dying of diabetes, computed from mortality statistics of the general population.[5a] On the basis of 1930 statistics for the United States, the probability of eventually dying from diabetes was slightly over 2% at age 10. For males it was 1.6% and for females 2.9%. The maximum figure for males was 1.8%, recorded about age 50, and for females 3.1% also about the same age. Even if one doubles the figures to allow for deaths of diabetics ascribed to

other causes, the highest figures at any age would not exceed 3.6% for males and 6.2% for females. These are far below the percentages recorded among the non-diabetic glycosurics, even within the short period of actual observation, namely, 9.9% for the experience as a whole and 15.5% among those 40 or over at first observation. The contrast would be even greater on the basis of the *eventual* incidence of diabetes among the non-diabetic glycosurics, because such incidence figures will be much higher than those for the relatively limited period of time elapsed since first observation.

Mortality. The mortality experience up to May 1, 1937, on these patients with non-diabetic glycosuria has been tabulated according to standard insurance practice, in the same manner as for diabetic patients of the clinic, previously reported.[55] Separate tabulations were made for cases coming first under observation prior to 1927 and since that time. The experience on the earlier cases was divided at 1927 to permit proper comparison of the experiences on earlier and more recent cases. The mortality of these patients was compared with that prevailing among insured lives. Because the experience covers a long period during which there has been a decided decrease in mortality of insured persons over most of the life span, separate mortality tables have been used to evaluate the experience prior to 1927 and since that date. In the earlier part of the experience, we have used the American Men (Ultimate) Table based upon standard insured lives during 1901 to 1916. For the years 1927 and later, we have used the Combined Annuity Table* for males which is based upon the mortality of clerks insured under group policies during 1922 to 1926. The earlier table excludes the so-called "select" period during which a low mortality exists because of medical selection. By its very nature, the later table has no "select" period. The comparative results are given in the form of ratios of actual deaths to the number expected if these patients had had the same mortality as experienced by insured lives.

On the basis of the insurance tables, the mortality of these non-diabetic glycosurics has been generally above the average. This is brought out by Table 14, which gives the ratios of actual to expected deaths, for the several divisions of the experience already described, at all ages combined, and in three broad attained age groups—under 45, 45 to 64, and 65 and over. For reasons stated below, the table gives data also for the experience with the first year after observation excluded.

For the experience as a whole, the mortality is about one-third higher than among insured lives. Patients seen prior to 1927 have

* Unfortunately no better insurance table covering the period between 1927 and 1937 is available. The table used, however, is a rather rigid standard, because the mortality of clerks is at most ages appreciably below the average for all employed persons.

had a relatively lower mortality than those first observed since that year. Among the earlier patients, at all ages combined, the mortality ratios before and since 1927 have been about the same.

Considered by age, the results were somewhat better under 65 than over that age. This has been true, however, only for patients first seen prior to 1927. In the more recent group, the ratios are higher, though not significantly so, under age 65 than over that age.

TABLE 14.—COMPARATIVE MORTALITY OF PATIENTS WITH NON-DIABETIC GLYCOSURIA AT ORIGINAL EXAMINATION. ACTUAL DEATHS AND RATIO TO NUMBER EXPECTED BY AMERICAN MEN (ULTIMATE) TABLE FOR EXPERIENCE PRIOR TO 1927 AND BY COMBINED ANNUITY TABLE (MALES) FOR EXPERIENCE SINCE 1927. TOTAL EXPERIENCE* AND EXPERIENCE EXCLUDING FIRST YEAR SEPARATELY. EXPERIENCE OF E. P. JOSLIN AND ASSOCIATES, 1900–1937.

Examination year; attained age.	Total experience.*						Experience excluding first year.					
	Per cent actual of expected deaths.			Actual deaths.			Per cent actual of expected deaths.			Actual deaths.		
	1900–May 1, 1937.	1900–1926.	1927–May 1, 1937.	1900–May 1, 1937.	1900–1926.	1927–May 1, 1937.	1900–May 1, 1937.	1900–1926.	1927–May 1, 1937.	1900–May 1, 1937.	1900–1926.	1927–May 1, 1937.
Total, 1900–1935												
All ages	133.8	.....	134.4	295	..	227	121.6	.....	124.5	245	..	198
Under 45	119.3	.....	132.7	37	..	27	118.8	.....	123.8	32	..	23
45–64	123.7	.....	122.4	132	..	96	102.9	.....	105.8	100	..	78
65 and over	152.2	.....	148.3	126	..	104	146.1	.....	145.4	113	..	97
1900–1926												
All ages	128.5	131.7	126.8	194	68	126	122.0	110.6	126.8	173	47	126
Under 45	106.3	93.8	119.5	22	10	12	114.2	107.8	119.5	21	9	12
45–64	112.5	127.2	103.9	86	36	50	100.5	93.6	103.9	72	22	50
65 and over	159.7	173.6	155.4	86	22	64	154.4	150.7	155.4	80	16	64
1927–1935												
All ages	.....	.....	145.2	...	..	101	.....	.....	120.7	...	..	72
Under 45	.....	.....	145.5	...	..	15	.....	.....	128.8	...	..	11
45–64	.....	.....	151.7	...	..	46	.....	.....	109.5	...	..	28
65 and over	.....	.....	138.3	...	..	40	.....	.....	129.3	...	..	33

* Excludes immediate mortality (*i. e.*, patients dying within 1 week of original observation).

These results, based upon the experience as a whole, include many patients who were seriously ill and in whom the glycosuria was an unimportant phase of cardiovascular and renal disease, cancer, hyperthyroidism and other serious conditions. On that account, the mortality in the first year especially was high, and if this is excluded, the results are distinctly more favorable. The mortality after the first year was, at all ages combined, approximately 20% above that expected by the standard tables.

Considered by age, the mortality ratios are generally highest past 65 and lowest between 45 and 64. The level of mortality except at the oldest ages is approximately that existing in substandard insurance risks.

Even the exclusion of the first year cases, however, does not give an accurate picture of the mortality of patients with uncompli-

cated non-diabetic glycosuria. Unfortunately, the data at hand do not permit complete segregation of such cases from those in which the glycosuria was incidental to other diseases. A review of the records, however, shows that a fairly large number had serious complications, such as cardiovascular disease, which would preclude them from insurance of any kind. High also was the incidence of overweight of sufficient degree to warrant limitation of many of these to substandard insurance on that account alone. Under these circumstances, the mortality results, excluding the first year experience, should be regarded as favorable and permit the conclusion that non-diabetic glycosuria in itself has little or no adverse influence on longevity.

Causes of Death. The majority of the deaths among these non-diabetic glycosurics resulted from cardiovascular and renal diseases, and in this group organic heart disease and coronary artery disease accounted for the largest number of deaths. The mortality from cancer was abnormally high, accounting for 19% of the deaths. Various types of infections, such as pneumonia, influenza, appendicitis and gall bladder disease, accounted for 10% of the deaths. No other cause of death was frequent.

In the foregoing, the deaths of those patients subsequently developing diabetes are included under the cause from which they died. The number of patients dying with diabetes was 48, or 15.5% of the total. Nearly two-thirds of the diabetics died of arteriosclerotic disease of the heart, kidney or vascular system. This proportion is distinctly higher than in the experience as a whole. No other single cause of death was prominent among the diabetics. *Not a single death was reported from diabetic coma.* Only 3 deaths were reported as due to diabetes without further details.

Table 15 shows the principal causes of death in the group as a whole. The table also gives the facts separately for those with and without diabetes. It includes 3 deaths discovered subsequent to May 1, 1937, the closing date of the mortality table in the preceding section.

The high mortality from cancer is significant.* Analysis according to site shows that 61% of the cancer deaths were primary digestive-tract cancers. This ratio is definitely above normal. Digestive-tract cancers accounted for 49% of all cancer deaths in the United States during 1932–1936 and for 46% of the cancer deaths among Industrial policyholders of the Metropolitan Life Insurance Comany during 1911–1935. The liver was involved in 11 cancer deaths in our series and the pancreas in 7 deaths, of which 5 were primary cancers of the pancreas. Approximately 40% of the cancer deaths occurred within a year of examination, as compared with only 15% for

* There is probably some bias in these data because of the close association of the George F. Baker Clinic with the Palmer Memorial, another division of the New England Deaconess Hospital, which had a relatively high proportion of cancer patients.

all other causes combined. A few of these patients were known to have cancer at first examination, or cancer was then diagnosed.

The proportion of first-year deaths was about the same for digestive and other cancers. Of the 11 deaths with cancer of the liver,

TABLE 15.—CAUSES OF DEATH AMONG PATIENTS ORIGINALLY DIAGNOSED AS NON-DIABETIC GLYCOSURICS. NUMBER AND PER CENT DYING FROM SPECIFIED CAUSES. ALL DEATHS AND DEATHS OF PATIENTS BECOMING DIABETIC AND THOSE REMAINING NON-DIABETIC SEPARATELY. EXPERIENCE OF E. P. JOSLIN AND ASSOCIATES, 1900–1937.

Cause of death.	All deaths.		Diabetics.		Non-diabetics.	
	Number.	Per cent.	Number.	Per cent.	Number.	Per cent.
All causes	310	100.0	48	100.0	262	100.0
Cardiovascular and renal diseases, total	171	55.2	31	64.5	140	53.4
Organic heart disease	56	18.2	11	22.8	45	17.2
Coronary artery disease	49	15.8	7	14.5	42	16.0
Chronic nephritis	15	4.8	2	4.2	13	5.0
Cerebral hemorrhage	33	10.6	5	10.4	28	10.7
Gangrene	6	1.9	3	6.3	3	1.1
Arteriosclerosis	12	3.9	3	6.3	9	3.4
Cancer	59	19.0	2	4.2	57	21.8
Diabetes	3*	1.0	3*	6.3	...	...
Tuberculosis	6	1.9	1	2.1	5	1.9
Infections, total	32	10.3	7	14.5	25	9.5
Accidents	8	2.6	1	2.1	7	2.7
Suicide	5	1.6	...	...	5	1.9
Other and not specified	26	8.4	3	6.3	23	8.8

* No further details.

TABLE 16.—CANCER DEATHS ACCORDING TO SITE AMONG NON-DIABETIC GLYCOSURICS, WITH SPECIAL REFERENCE TO INVOLVEMENT OF THE LIVER AND PANCREAS. DEATHS WITHIN A YEAR OF FIRST OBSERVATION SEPARATELY. EXPERIENCE OF E. P. JOSLIN AND ASSOCIATES, 1900–1937.

Site of cancer.	Number of deaths.	
	Total cases.	First year cases.
Total	59	24
Digestive tract and peritoneum, total	36	15
Esophagus	1	..
Stomach	12	6
Intestines	9	2
Rectum	3	1
Liver	5	2
Pancreas	5	4
Peritoneum	1	..
Breast	6	1
Other and not specified	17	8
Liver, including metastatic	11*	4
Pancreas, including metastatic	7*	5

* One case pancreatic and hepatic involvement, secondary to cancer of stomach.

4 occurred in the first year; and of the 7 with cancer of the pancreas, 5 were first-year deaths.

There were only 2 cancer deaths among patients who became diabetic, one from an "abdominal" cancer 4 years after first observation and 1 from cancer of the colon, 14 years after first observation. The details regarding cancer are given in Table 16.

Discussion. The data of this paper demonstrate that glycosuria of significant degree (over 0.3%), particularly if found on more than one occasion, must not be dismissed lightly. One must remember that these 1,946 patients were part of a much larger group of 14,000 individuals with glycosuria, of whom the vast majority were diagnosed as true diabetics at initial observation. Caution must be taken in diagnosis and advice to the patient, even though random blood sugar values are within normal limits. Usually the glycosuria remains benign; but, nevertheless, of these 1,946 patients, thought at initial observation not to be diabetic, 9.9%, over a period of subsequent observation averaging nearly 9 years, have shown characteristics compatible with the diagnosis of diabetes. Moreover, the probability of the development of diabetes later in life is far greater for these patients than for the population at large.

With individuals, then, exhibiting glycosuria, how can one detect those who have mild diabetes or foretell those who stand the greatest chance of later developing diabetes? This experience affords certain clues. In the first place, the glycosuria is most likely to be significant, if the individual is or has been overweight, if he is over 40 years of age and if he is Jewish. The presence of diabetes in a near relative is of some, though less, importance. In the second place, if random blood sugar values are borderline or slightly above average, the glycosuria takes on added significance. If special studies, such as sugar tolerance tests, are carried out, particularly with individuals possessing one or more of the above characteristics, latent or mild diabetes may be detected in a sizable percentage. Thus the diagnosis was subsequently changed in only 6.3 per 1,000 per annum among those studied with glucose tolerance tests, as compared with 12.6 per 1,000 per annum in patients not "adequately" studied.

Certain aspects of the group with changed diagnosis are significant and reassuring. The diabetes developed by most of these patients is relatively mild. None has died in diabetic coma. Only 73 of the 193 patients have taken insulin at any time up to the present. In some instances, the diabetes was so mild as to be demonstrable only by a sugar tolerance test.

Particularly with individuals in or past middle life, glycosuria may accompany and thus even suggest a degenerative disease of more seriousness than diabetes, so far as duration of life is concerned. Of the 310 deaths in the present series, 65, or over 20%, took place within a year of the first observation usually from such diseases

as cardiovascular or renal disturbances, cancer or infections. In so far as the data permit a conclusion, non-diabetic glycosuria in itself seems to have little or no adverse influence on longevity.

Sugar tolerance tests are fallible. Whether the test be of the standard type using varying amounts of glucose or whether it be of a special variety such as the "one-hour two-dose" tolerance test,[1] the curve must be interpreted in the light of various factors. Carbohydrate tolerance may be temporarily lowered by an infection or toxemia, by starvation or a low starch diet and by the giving of insulin. Furthermore, age has a definite influence. Glycosuria or hyperglycemia may at times be found in various conditions, among which are hypertension, nephritis, pregnancy, hyperthyroidism, diseases of the liver, the pituitary and the adrenals, cancer, gallbladder disease, obesity and arthritis.

In carrying out tolerance tests, the following points in the technique are essential for dependable results.

1. The sugar solution should be made as palatable as possible and not be of more than 20% concentration. The patient must take the full dose of sugar prescribed, must retain it and not be appreciably upset by the procedure.

2. The test should be done after a fast of at least 5 hours and preferably 12 hours. This conservative minimum has been adopted by the George F. Baker Clinic, because curves at shorter intervals after food may be bizarre and give misleading results.

3. To make certain that no febrile illness exists, the body temperature should be taken before the beginning and after the end of the test.

4. Blood must be collected in such manner as to prevent clotting and as to preserve the sugar content.

5. Tests should be done under competent supervision. More than one unusual result has been traced to a laboratory error. If the result given does not agree with the clinical findings, the test should be repeated.

Melituria Other Than Glycosuria. As an addendum to this presentation, brief comment is necessary regarding those cases of normoglycemic melituria in which the urinary sugar is not glucose but lactose, galactose, fructose or pentose. In every individual with melituria proved not to be diabetic, the type of sugar excreted should be identified with the aid of special tests, including the fermentation test, reduction with Benedict's solution at temperature below 60° C., Seliwanoff's and Bial's tests, and the formation of the respective osazones with characteristic melting points. The series in this paper includes 4 cases of pentosuria and 1 of levulosuria. Such cases are most commonly found among Jewish males. Often the diagnosis of diabetes is made in these patients, then later changed to renal glycosuria and then finally, perhaps after many years have elapsed, the true diagnosis is made. There is, of course,

no connection between these meliturias, other than glycosuria, and true diabetes.

Conclusions. 1. Of 2,065 patients seen from 1900 to 1935 who at first observation were thought to have non-diabetic glycosuria, all but 1.5% were traced as of May 1, 1937. The condition of the patients was ascertained at the time of tracing. After certain exclusions, 1,946 cases remained on which this study was based.

2. Of the total of 1,946 patients, 1,142 are males and 804 females. Living cases number 1,636 and fatal cases 310.

3. In 193 cases (9.9% of the total) true diabetes has developed. In most instances the diabetes was mild. No case of renal glycosuria, as strictly defined above, has progressed to diabetes.

4. Factors favoring diabetes were, in approximately the order named, advancing age, overweight, blood sugar values above the average normal at first observation (though below a definitely diabetic level) and in the younger patients a family history of diabetes. The percentage becoming diabetic rose with increasing duration since initial observation. It was higher in Jewish than in non-Jewish patients.

5. Adequate study at initial observation, particularly with postprandial blood sugar tests and glucose tolerance tests, increased greatly the chances of distinguishing diabetic from non-diabetic glycosuria.

6. Among 310 fatal cases, 262 deaths were of patients whose glycosuria remained benign, but a significant proportion of these deaths occurred within a year of first visit. Both among those becoming diabetic and those remaining non-diabetic, the incidence of deaths from cardiovacular and renal diseases was strikingly high. The incidence of cancer as a cause of death was five times as high in the non-diabetic as in the diabetic group. There was no death from diabetic coma.

7. Glycosuria, apart from diabetes, may be an accompaniment and a warning sign of degenerative disease and thus be of unfavorable diagnostic import.

8. In the absence of complications, non-diabetic glycosuria seems to exert little or no adverse influence on length of life.

9. Diagnostic standards and procedures, particularly as regards sugar tolerance tests, are discussed.

10. The desirability of recognizing cases of pentosuria and fructosuria is stressed.

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WHY DIABETICS DISCONTINUE PROTAMINE INSULIN.

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The first 1250 patients of this clinic to take protamine insulin in one form or another between August, 1935 and April 1937, were followed up in the spring of 1938 and 1222 (97.7%) were traced. A preliminary report of the results of a study of these cases has already been made[1a] and a second paper will be given soon.[1b] Of the entire group, 102 had discontinued protamine insulin, 7 of them temporarily. To analyze their reasons for giving up protamine insulin is the object of this paper. The data are given in detail below.

Table 1.—Reasons for Abandoning Protamine Insulin.

Reason.	Patients. No.	Per cent.
Sugar-free without insulin	41	43.1
Hypoglycemic reactions	33	34.7
Local allergic responses	3	3.1
Uncoöperative	5	5.3
Poor diabetic control	5	5.3
Advice of home physician	4	4.2
Irregular mode of living	2	2.1
Insufficient time for adjustment	1	1.1
No reason apparent	1	1.1
	95	100.0
Discontinued, later resumed	7	
	102	

Seven patients who gave up *protamine zinc insulin* for one cause or another are now using it again. It must be remembered, particularly with regard to the patients who started it in 1935, that protamine insulin was then a new discovery and its effects were inadequately understood. Thus, one of the diabetic children was originally adjusted to *protamine zinc insulin* at a summer camp and went from there to the Philippine Islands. Her mother did not receive instruction in the management of diabetes such as she would have received had her daughter been in the hospital. The child had severe hypoglycemic reactions and the mother shifted her back to unmodified insulin. This summer the patient has been at a diabetic camp again for several weeks, receives *protamine zinc insulin* along with the rest of the youngsters and has been well and free from reactions.

The largest number of the group, 41, is made up of those who are sugar-free without insulin when on a careful diet and under normal circumstances. A few of them take small quantities of insulin occasionally, but most of them get along well without it.

Hypoglycemic reactions with *protamine zinc insulin* are responsible for the largest group of diabetics, 33, who have resumed regular (unmodified) insulin. The symptoms have varied in severity from mild, constant fatigue, headaches, nervousness or nausea to rare complete unconsciousness. This group includes both mild and severe diabetics. Most of these 33 patients write that they are happier and freer from reactions now that they have returned to the old insulin. Many of them state that they varied between marked glycosuria and hypoglycemic reactions and add that if they took enough insulin to clear up the urinary sugar, reactions ensued. Many of them found that the insulin shock with protamine insulin was more severe than with regular insulin. Of the 78 deaths (among the total of 1250 cases) reported up to June 9, 1938, however, none seemed to their home physicians or the writer to be attributable to *protamine zinc insulin*.

In 3 cases, local allergic responses, painful and indurated areas at the site of injection, caused patients to discontinue protamine insulin. In no instance, except in one doubtful case, did an abscess result.

It was impossible to secure the coöperation of 5 patients. Two of this number were definitely psychotic and it was felt that the other 3 were too unintelligent to learn how to use the new preparation properly.

Another group of 5 patients were definitely able to control their diabetes better with the old insulin than with *protamine zinc insulin*. It is possible, however, that even with these patients hospitalization and careful study might enable one to control their diabetes with protamine insulin or with a combination of regular and protamine.

Four diabetics were changed back to regular insulin because their local physicians believed it preferable in their particular cases. Another 2 patients lead irregular lives, changing back and forth from day to night work and are better controlled on the old insulin. One patient was started on *protamine zinc insulin* at the hospital but left before the adjustment had been satisfactorily made. In one case no reason for discontinuing *protamine zinc insulin* was apparent.

Discussion. It is evident from the above that if those patients are excluded who now require no insulin for control of diabetes and those who later resumed protamine insulin, only 54 (4.4%) of the 1222 traced have discontinued the slowly acting preparation. Of these 54, 5 were uncoöperative and others gave it up for reasons which seem inadequate. Furthermore, experience gained during the past 3 years has demonstrated that hypoglycemic reactions, which led 33 patients to discontinue protamine insulin, need be no more frequent, if as frequent, with the new as with the unmodified insulin. Avoidance of reactions is achieved in almost all cases by recognition of the fact that when one uses *protamine zinc insulin* once daily

before breakfast, a normal fasting blood sugar value precludes further increase in dosage. If more insulin is needed to control hyperglycemia during the course of the day, the unmodified type must be used. In almost all cases, this may be given as an accompaniment of the protamine insulin before breakfast with no more insulin of any sort during the rest of the day. The blood sugar value in the late forenoon serves as an index of the effect of the unmodified insulin.

Conclusion. At the very outside, therefore, the number of diabetic patients who cannot use *protamine zinc insulin* successfully and to great advantage is less than 5%; and, allowing for the factors discussed above, is probably much less than this low figure. Certainly we should not withhold protamine insulin from the great mass of diabetics merely because an occasional patient seems not to do well with its use.

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(1.) **Joslin, E. P.**: (*a*) J. Am. Med. Assn., **109**, 497, 1937; (*b*) Protamine Insulin; paper read at Gesellsch. f. Verdauungs. u. Stoffwechselkrankh., Stuttgart, September 22, 1938.

BOOK REVIEWS AND NOTICES.

THE RHEUMATIC DISEASES. A Course of Lectures Arranged by The Medical Staff of the St. John Clinic and Institute of Physical Medicine. Edited by SIR LEONARD HILL, M.B., LL.D., F.R.S., Director of Research, St. John Clinic and Institute of Physical Medicine and Consultant to the Rheumatic Unit at St. Stephen's Hospital (London County Council), and PHILIP ELLMAN, M.D., M.R.C.P., Physician to St. John Clinic and Institute of Physical Medicine and Consultant to the Rheumatic Unit at St. Stephen's Hospital (London County Council). With a Foreword by SIR ARTHUR MACNALTY, K.C.B., M.D., F.R.C.P., Chief Medical Officer to the Ministry of Health. Pp. 270; 46 illustrations. Baltimore: William Wood & Co., 1938. Price, $4.00.

THIS book is a symposium by 15 contributors; as explained by the Editor in the preface it is based upon a "course of weekly lectures on Rheumatic Diseases. . . . . In a volume of this kind, written by individuals on closely related subjects, some degree of overlapping is inevitable . . . . any divergence of opinion observed by the reader is not without merit in the present limited state of our knowledge." The book is divided into 20 chapters or articles, exclusive of the foreword, covering such topics as the social and economic aspects of Rheumatic Diseases, classification, pathology, focal infection, radiology, serology, non-articular rheumatic affections and treatment. For the most part, the views expressed are those familiar to readers of the American literature on the subject. The articles show a trend of opinion toward the view that rheumatic fever and rheumatoid arthritis are different forms of the same pathologic process. The infectious nature of "rheumatoid arthritis" seems to be conceded by most of the contributors, with due appreciation of other etiologic factors involved. A few of the opinions expressed are a little startling; for instance, C. A. Robinson says "I hold that chronic infective arthritis in women is due, in the vast majority of cases, to an infected cervix." Fibrositis is described as a very common condition, but the explanation of its pathologic physiology is rather vague. The section on physical therapy comprises nearly a quarter of the book. The importance of orthopedic treatment is stressed but detailed descriptions are necessarily lacking; the beneficial results of arthrotomy and lavage are repeatedly mentioned.

The paper, print and illustrations are good. This little book is, in general, both sound and pleasant. However, the Reviewer believes that it does not fill any important need of American readers; as a review course for either the general internist or the family practitioner, he prefers the summaries of current literature on arthritis and allied diseases which are published annually in periodicals. J. C.

PEDIATRIC SYMPTOMATOLOGY AND DIFFERENTIAL DIAGNOSIS. By SANFORD BLUM, A.B., M.S., M.D., Head of Department of Pediatrics and Director of the Research Laboratory, San Francisco Polyclinic and Post Graduate School. Pp. 500; 29 illustrations, including 1 colored plate. Philadelphia: F. A. Davis Co., 1938. Price, $5.00.

USING terse, direct sentences, the author presents the symptoms and physical features of the multitudinous ailments of children. Etiology,

pathology, prophylaxis and therapeutics are as a rule not touched upon. Roentgenology and clinical laboratory methods receive brief and inadequate mention. Some illustrations are included. The index consists mainly of the names of diseases; symptoms are listed but rarely. The usefulness of this volume appears restricted to those fact-loving physicians who desire a handy volume in which they can look up the information there contained.

I. W.

MARIHUANA. AMERICA'S NEW DRUG PROBLEM. A Sociologic Question With Its Basic Explanation Dependent on Biologic and Medical Principles. By ROBERT P. WALTON, Professor of Pharmacology, School of Medicine, University of Mississippi. With a Foreword by E. M. K. GEILING, Professor of Pharmacology, University of Chicago, and a Chapter by FRANK R. GOMILA, Commissioner of Public Safety, New Orleans, and M. C. GOMILA LAMBOU, Assistant City Chemist. Pp. 223; 13 illustrations. Philadelphia: J. B. Lippincott Company, 1938. Price, $3.00.

WHAT to the farmer is known as a weed, in history is known as hashish, in medicine as cannabis sativa, and in an Act of Congress, as marihuana. This monograph, which is a fair appraisal of the marihuana problem, shows that titles such as the "Flower of Hell" and "Marihuana—Assassin of Youth," suggest capacity for harm that are misleading. Some of the contents of the volume describe the history of the hashish vice and its distribution; present status of the vice in the United States; botanical consideration; hashish experience includes literary, subjective, objective and psychiatric descriptions; acute and chronic effects; therapeutic applications; pharmaceutical and chemical considerations. So unpredictable is its action, that marihuana has been called "the coquette of drugdom." Plants growing side by side may vary vastly in potency; when all other conditions are the same, the effects upon 2 persons may be opposite, and upon the same person, they may differ greatly at different times. Our own Bayard Taylor, who desired first-hand information, while once in the Orient, decided to learn the subjective effects of hashish; by mistake, six times the usual quantity was taken, and his description of its acute effects is a classic; full recovery testifies to the frequent statement that there probably are no authentic instances of fatalities. Marihuana's fame as an aphrodisiac is not fully justified. With us, indulgence is usually in the form of cigarettes, known in the vernacular as "reefers;" the smoke is always inhaled and retained for considerable time. The smoker is usually aware of increasing energy and power; often there is excitement, with the user realizing that his thoughts and actions are coming less under control; faces of those about may assume grotesque expressions, or the subject may be seized with unprovoked laughter, realizing at the time its ridiculousness; lengthening of time and space is usually experienced, and double consciousness may be present. Its use does not enslave as does opium; if one speaks of the latter as causing addiction, perhaps one should say the use of marihuana leads to habituation. Its relation to crime is similar to that of alcohol, neither producing crime directly, but through releasing inhibitions, tendencies usually under restraint may then become active. After preparations of marihuana have been smoked, or ingested, daily in large quantities, and over long periods of time, its users show some degree of permanent mental impairment. There is a classified bibliography of more than 17 pages, an extensive author index and an informative general index.

N. Y.

AVIAN TUBERCULOSIS INFECTIONS. By WILLIAM H. FELDMAN, D.V.M., M.S., Associate in Division of Experimental Medicine, Institute of Experimental Medicine; Associate Professor of Comparative Pathology, The Mayo Foundation for Medical Education and Research, Graduate School, University of Minnesota. Pp. 483; 109 illustrations. Baltimore: The Williams & Wilkins Company, 1938. Price, $7.00.

As the author states in his preface, avian tuberculosis, except by those especially interested in comparative medicine, is a poorly understood field. Veterinarians are well acquainted with its practical aspects; practising physicians, on the other hand, are almost unacquainted with the problem or the light that its understanding can throw on the general problems of tuberculosis. This book—written in order to provide a convenient source of knowledge of avian tuberculosis, useful alike to veterinarians, experimental pathologists, teachers and physicians—successfully fulfils its purpose.

The monograph opens with an interesting review of the extent and importance of avian tuberculosis, which is a major hazard in an industry valued at $2,000,000,000 annually in the United States. While the disease is widely distributed throughout the country, its greatest concentration occurs in the north central states, where about 50% of flocks and 3 to 6% of chickens are infected.

The book proceeds, with good organization and an easy, clear style, to chapters on laboratory procedures in the understanding of avian tuberculosis, the pathology of the disease, the pathogenicity of the avian bacillus, and the control of its dissemination. A bibliography is attached to each chapter.

The section on laboratory methods is notable in combining an excellent review of the subject in broad aspect with explicit instructions for the important procedures of isolation of the bacillus, typing for pathogenicity and tuberculin testing. The chapters on the pathologic anatomy of avian tuberculosis in its spontaneous and experimental forms are comprehensive and well illustrated.

The chapters on the pathogenicity of the avian tubercle bacillus for the various animal species are among the most valuable, for it is in this field that general knowledge is most lacking. The important question of pathogenicity for swine is discussed at length, with its bearing on the epidemiology of the disease in chickens. Naturally physicians will be especially interested in Feldman's review of the reported cases of avian bacillus infection in man. He lists 37 reported cases, but regards not more than 13 as valid. As he states, in view of man's opportunity for infection, the rarity with which he develops lesions indicates a formidable resistance. Feldman considers the evidence of an etiologic rôle of the bacillus in Hodgkin's disease quite unconvincing.

A final chapter appropriately takes up the subject of control of dissemination of the disease in poultry. E. L.

CLASSIC DESCRIPTIONS OF DISEASE. With Biographical Sketches of the Authors. By RALPH H. MAJOR, M.D., Professor of Medicine, University of Kansas School of Medicine. Pp. 727; illustrated. Second edition. Springfield, Ill.: Charles C Thomas, 1939. Price, $5.50.

THE second edition of this excellent medical anthology is especially welcome as enough new material is included to make it distinctly more valuable than the first. It has proved possible, without greatly increasing the size of the book, to include 27 more original accounts by 11 more authors than in the first edition. Among the most important are 9 descriptions of malaria, ranging from Aristophanes to Ronald Ross, the Yellow Fever

accounts of Matthew Carey, Benjamin Rush, Carlos J. Finlay and Walter Reed; W. S. Kirkes' account of pyemia resulting from (subacute bacteria) endocarditis; Koplik's spots; Heberden's nodes; a case of allergy from Jenner's *Inquiry;* and parts of Withering's account of foxglove. New Lives and Illustrations are equally in evidence, so that it becomes ungracious to wish that still others might have been included that now remain conspicuous by their absence! Except for a good textbook of medical history, we know of no single volume on the subject that should be more interesting or instructive to physicians of all kinds. Readers should not be confused by the accidental omission of the title "Plague" and of references to Thucydides and Rufus in the Table of Contents. E. K.

CARDIOVASCULAR DISEASE IN GENERAL PRACTICE. By TERENCE EAST, M.A., D.M. (OXON.), F.R.C.P. (LOND.), Physician and Physician-in Charge of Cardiological Department, King's College Hospital; Physician, Woolwich War Memorial Hospital, etc. Pp. 206; 43 illustrations. London: H. K. Lewis & Co., Ltd., 1938. Price, 10s. 6d; Philadelphia: P. Blakiston's Son & Co., 1939. Price, $3.50.

THIS little book is one of a series issued by the publishers, called "The General Practice Series. The subject is as completely covered as could be expected in a book of this size. It is recommended for those practitioners who wish to consult an elementary discussion of cardiovascular disease. In the opinion of the Reviewer, however, it is a little too elementary, and does not include enough discussion of the details of treatment, to be useful to most American practitioners. C. W.

THE SURGERY OF ORAL AND FACIAL DISEASES AND MALFORMATIONS. Their Diagnosis and Treatment Including Plastic Surgical Reconstruction. By GEORGE VAN INGEN BROWN, D.D.S., M.D., C.M., F.A.C.S., Emeritus Professor of Plastic Surgery, University of Wisconsin; Plastic Surgeon, Children's, St. Mary's, Columbia, and Milwaukee County Hospitals, Milwaukee; State of Wisconsin General Hospital, Madison, etc.; Colonel, Inactive Reserve, United States Army. Pp. 778; 589 engravings containing 1019 illustrations and 12 colored plates. Fourth edition, thoroughly revised. Philadelphia: Lea & Febiger, 1938. Price, $10.00.

EACH successive appearance of this work, which was first published in 1912, reflects the great strides that have been made in the surgery of this part of the body over a period of about 25 years. The book is not limited to surgery, but covers also many of the manifestations of skin and general diseases about the face and mouth. With few exceptions, the views expressed in this section are in accord with accepted teaching. In the treatment of erysipelas and actinomycosis, it is surprising to note that no mention is made of irradiation. The chapter on tumors of the mouth and and jaws, and especially the section dealing with the growths arising from dental issues, cannot be said to be well systematized, and is likely to be confusing to the student.

The author's wide experience with harelip and cleft palate fully justifies the space devoted to this subject. In general, his views on the principles of treatment of this deformity are in accord with those of most present-day surgeons in this field. He discusses at length the advantages of the "bone-flap operation" in cleft palate as compared to the use of mucoperiosteal flaps alone.

In this fourth edition the chapters on plastic surgical restoration of facial deformities form a noteworthy contribution to the literature of the subject, and are perhaps the outstanding feature of the book. R. I.

SURGICAL PATHOLOGY OF THE DISEASES OF THE MOUTH AND JAWS. By ARTHUR E. HERTZLER, M.D., Surgeon to the Agnes Hertzler Memorial Hospital, Halstead, Kansas; Professor of Surgery, University of Kansas. Pp. 248; 206 illustrations. Philadelphia: J. B. Lippincott Company, 1938. Price, $5.00.

THIS is the last of the author's 10 volumes on surgical pathology; in his characteristic phrase, "after thirty-five years of writing I shall trade my pen for a lollipop." He recognizes difficulties with his subject, especially for the two reasons that this field has moved from the hands of "general practitioners like myself" to those of specialists and dentists; and also because he is forced to describe many things that he has not seen. In regard to the literature, he has "adopted the more respected practice of having my secretary copy them out of the Cumulative Index!"

E. K.

NEW BOOKS.

Elementary Anatomy and and Physiology. By JAMES WHILLIS, M.D., M.S., F.R.C.S., University Reader in Anatomy, Guy's Hospital Medical School; late Lecturer in Anatomy in the University of Durham. Foreword by T. B. JOHNSTON, M.D., CH.B., Professor of Anatomy, University of London. Pp. 342; 87 illustrations, prepared from original drawings by Pauline Lariviére. Philadelphia: Lea & Febiger, 1939. Price, $3.50.

The Patient is the Unit of Practice. By DUANE WILLARD PROPST, A.B., B.S., M.D., Assistant Professor of Medicine, University of Illinois College of Medicine. Pp. 219; 4 plates. Springfield, Ill.: Charles C Thomas, 1939. Price, $3.50.

The Diagnosis and Treatment of Diseases of the Thyroid. By JAMES H. MEANS, M.D., Jackson Professor of Clinical Medicine, Harvard University, and Chief of the Medical Services, Massachusetts General Hospital, and EDWARD P. RICHARDSON, M.D., John Homans Professor of Surgery, Harvard University, and Chief of the West Surgical Service (Massachusetts General Hospital). (Reprinted from Oxford Monographs on Diagnosis and Treatment.) Pp. 367; 51 illustrations. New York: Oxford University Press, 1938. Price, $5.00.

Fluorine Toxicosis in the Albino Rat. (Research Bull. 247, Agricultural Experiment Station, Iowa State College of Agriculture and Mechanic Arts). By J. A. SCHULZ. Pp. 242; 1 figure and 28 tables. Ames, Iowa: Iowa State College of Agriculture, 1938.

Ueber die Integrative Natur der Normalen Harnbildung, Teils I, II, III (Teil III. Systematischer Rückblick). By GÖSTA EKEHORN, D:R. Med., Stockholm. Pp. 1429. Helsingfors: Printed by Mercators Tryckeri, 1938.

Proceedings of Meetings of the New York Pathological Society held October 28, November 18 and December 23, 1937; January 27, February 24, March 29, April 28 and May 26, 1938. (Reprinted from Archives of Pathology.) Pp. 46; 2 illustrations.

Clinical and Experimental Investigations in Agranulocytosis. With Special Reference to the Etiology. By PREBEN PLUM. Pp. 410; 125 illustrations, many in color. London: H. K. Lewis & Co., Ltd., 1937.

Die endokrinen Drüsen des Gehirns, Epyphyse und Hypophyse. Ein Blick in ein interessantes Gebiet. By DR. MED. PAUL NIEHANS, Chirug. F. M. H. der Klinik von Clarens und der Spitäler von Vevey und Montreux (Schweiz). Pp. 280. Bern: Medizinischer Verlag Hans Huber, 1938. Price, Fr. 10.50.

St. Thomas's Hospital Reports, Second Series, Vol. III. Editors: Prof. O. L. V. S. De Wesselow, Mr. C. Max Page, assisted by Mr. N. B. Barrett, Dr. J. St. C. Elkington, Dr. A. J. Wrigley. Pp. 240; many illustrations. London: Headley Brothers for St. Thomas's Hospital, 1938. Price, 7s. 6d. (after publication 10s. per volume).

William B. Wherry, Bacteriologist. By Martin Fischer. Pp. 293; 21 illustrations. Springfield, Ill.: Charles C Thomas, 1938. Price, $4.00.

Surgical Treatment of Hand and Forearm Infections. By A. C. J. Brickel, A.B., M.D., Departments of Anatomy and Surgery, Western Reserve University. Pp. 300; 166 illustrations and 35 plates (10 in color). St. Louis: The C. V. Mosby Company, 1939. Price, $7.50.

Richtlinien Praktischer Orthopädie. By Dr. Albert Lorenz. Pp. 464; 123 illustrations. Wien: Franz Deuticke, 1939. Price, Paper, M. 15; Bound, M. 16.80.

Recipes and Menus for Allergics. By Myra May Haas. In Collaboration with Nathan Schaffer, M.D. Menus by Cay Hillegas. Illustrations by O. Soglow. Pp. 250; illustrated. New York: Dodd, Mead & Co., 1939. Price, $2.50.

Medicine in the Outpatient Department. An Introductory Handbook. By Winthrop Wetherbee, Jr., M.D., Junior Visiting Physician, Boston City Hospital. With a Foreword by George R. Minot, M.D., S.D., F.R.C.P. (Edin. and Lon.), F.A.C.P., Professor of Medicine, Harvard University; Director, Thorndike Memorial Laboratory; Visiting Physician, Boston City Hospital. Pp. 111. New York: Paul B. Hoeber, Inc., 1938. Price, $1.00.

Cardiovascular Disease in General Practice. By Terence East, M.A., D.M., Oxon., F.R.C.P. Lond., Physician and Physician-in-Charge of Cardiological Department, King's College Hospital; Physician, Woolwich War Memorial Hospital, etc. Pp. 206; 43 illustrations. Philadelphia: P. Blakiston's Son & Co., Inc., 1939. Price, $3.50. (Review p. 563).

Clinical Bacteriology. By F. A. Knott, M.D., M.R.C.P., D.P.H., Director, Bacteriological Department and Lecturer in Bacteriology, Guy's Hospital. Pp. 426; 60 illustrations, including 12 plates. Philadelphia: P. Blakiston's Son & Co., Inc., 1939. Price, $4.50.

Consolidated Indices. Embracing Transactions of the American Roentgen Ray Society (1903–1908); American Quarterly of Roentgenology, Vols. I–V (1906–1913); American Journal of Roentgenology, Vols. I–IX (1913–1922); American Journal of Roentgenology and Radium Therapy, Vols. X–XXXVIII (1923–1937). Author and Subject: 1903–1937. Compiled under the direction of the Publication Committee and the Editorial Office of the American Roentgen Ray Society, 1939. Pp. 451. Springfield, Ill.: Charles C Thomas, 1939. Price, $12.50.

The New International Clinics, Vol. I, N.S. 2, 1939. Edited by George Morris Piersol, M.D., Professor of Medicine, Graduate School of Medicine University of Pennsylvania, Philadelphia. With 18 Collaborators. Pp. 312; illustrated, also 1 colored plate. Philadelphia: J. B. Lippincott Company, 1939.

The current number contains 15 original contributions on a variety of subjects, together with clinics from Dr. Eliason's and Dr. Lee's service, and a review of recent progress on water balance; edema and dehydration by Cantarow.

Bacteria. The Smallest of Living Organisms. By Dr. Ferdinand Cohn (1872). Translated by Charles S. Dolley (1881). Introduction by Morris C. Leikind. Pp. 44; 4 illustrations. Baltimore: The Johns Hopkins Press, 1939. Price, $1.00.

PROGRESS
OF
MEDICAL SCIENCE

GYNECOLOGY AND OBSTETRICS.

UNDER THE CHARGE OF
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PROLAPSE OF THE UTERUS.

ALTHOUGH uterine prolapse has been recognized and treated since the days of prehistoric woman, it has only been within recent years that gynecologists have seriously studied the causes of this condition and outlined rational methods of treatment. There are so many theories concerning the mechanism of uterine support that Mengert[13] has attempted a quantitative evaluation of the relative importance of the various uterine supports. He took 8 female cadavers, none of which had uterine prolapse and after attaching a 1-kg. weight to the cervix, the paired structures attached to the uterus were severed in varying sequences and the resulting uterine descent measured. It was found that section of the round, ovarian, infundibulopelvic and the upper third of the broad ligaments hardly affected the position of the uterus in the pelvis. The pelvic floor, although it was never incised, did not hinder experimental prolapse of the uterus, and therefore could not have contributed to uterine support in any of the 8 subjects. Section of the parametrial and upper two-thirds of the paravaginal tissues allowed an average uterine descent of 10.5 cm. Marked descent of the uterus amounting to actual prolapse never occurred so long as any part of the upper two-thirds of the paravaginal or lower two-thirds of the parametrial tissues were intact and of these two tissues the paravaginal tissue seemed to be slightly more important, for its division allowed an average uterine descent of 6.9 cm? as compared with 3.6 cm. following division of the parametrial tissues. These paravaginal structures which are so important are also known as cardinal ligaments and are of great importance in the operative correction of prolapse as will be discussed later.

Although injury to the paravaginal tissues is of great importance in the etiology of prolapse, it does not explain the instances of prolapse

in nulliparous women or even virgins in whom there has never been any vaginal trauma. As a result of some study which Laws[11] has made, he believes that in many of these cases there is a spina bifida occulta, which involves the fourth sacral nerve with consequent paralysis of the levator ani muscles. This condition may also account for early recurrence of prolapse after operation, as he found in 3 of his cases. He states that in these cases the symptoms of prolapse may be absent until adult life and then be considered as entirely due to childbirth injuries.

The surgical management of prolapse has been well outlined by Phaneuf,[15] who states that three factors determine the method of operation to be chosen in the given individual, namely, the age of the patient, the possibility of future pregnancies and finally, the extent of the prolapse. Uterovaginal prolapse in young women during the childbearing age may be satisfactorily treated by repairing the cervix, the anterior and posterior vaginal walls and the perineum, by shortening the uterosacral ligaments and by performing a round ligament suspension of the uterus. After the menopause one of the vaginal methods is given the preference because of increased operability because of lessened morbidity and mortality. An abdominal incision is made in only a limited number of cases, to obliterate a very large posterior vaginal hernia. The interposition operation (Watkins-Wertheim) followed by amputation of the cervix has given him excellent results and has been his favorite method of treatment, but we will have more to say about this operation later. Vaginal hysterectomy with interposition of the united broad ligaments is reserved for women with atrophied uteri and when malignancy is suspected. In feeble old women, where an extensive vaginal operation is contraindicated, either total colpectomy or the subtotal operation of LeFort may render great service, especially when performed under local anesthesia. It is important that an adequate repair of the pelvic floor be made in all cases except in nulliparous women where the perineum is intact and gives good support. Having thus outlined the general principles in the selection of a suitable operation, it will be of interest to discuss in more detail some of the more common procedures.

Manchester-Fothergill Operation. This operation which was devised by the Manchester group of gynecologists and popularized by Fothergill is based primarily upon shortening the cardinal ligaments by reefing them anterior to the uterus by a vaginal approach. It is curious that this operation has been done for years in England with satisfactory results, but has only recently been taken up in our country. From a survey of the literature it is apparent that it is being widely employed and, on the whole, the results have been quite satisfactory. Shaw[18] reports a series of 549 cases in which this operation produced cures in 95%. Being from Manchester his article can be considered authoritative concerning the proper technique of the operation, which will not be discussed in detail in this review, but which should be consulted by those who intend to perform the operation without previous experience. He believes that the operation is the best one for all patients with prolapsus, whether young or old, nulliparous or parous and it is not followed by any difficulty in subsequent labors. The prolapse may recur after subsequent labors in less than 25% of the cases. He says

that it is necessary to combine an abdominal operation with the colporrhaphy only in those very rare cases where practically no muscular tissue is found in the pelvic floor and in his series it was used only in 2 cases. Salmon[17] reports a series of 254 cases in which this operation was used, with only 1 recurrence. In 15 cases there was considerable sagging of the anterior vaginal wall but even in these the cervical stump and fornices remained high up during straining. The operation was put to its severest test in the cases of recurrent prolapse following the interposition operation and ventrofixation and in a group of 8 cases of prolapse of the cervical stump occurring after supravaginal hysterectomy. The universally excellent results in this group were very gratifying. While the English schools feel that the operation is no contraindication to subsequent pregnancy, he believes that pregnancy should be avoided, and it has been his practice to ligate the Fallopian tubes through the vagina in those patients who are still menstruating. In a series of 152 cases reported by Gordon,[10] amputation of the cervix was not done in 50 of them, although this is usually considered a part of the operation. Local anesthesia was used almost routinely after preoperative medication with barbiturates and morphine and in this way it was not necessary to reject poor risks. He has found that slight bleeding about the sixth or seventh day and a foul vaginal discharge are commonly seen and he had 8 cases which were complicated by pelvic cellulitis. Every patient in the series was cured of her prolapse after at least a 2-year observation, although in a small number there were slight residual symptoms which could usually be cured by a minor operation. Even if those with minor symptoms were classified as failures, the curability rate in this series was over 96%. Four patients have had 1 baby since the operation and 2 have been delivered twice; in 1 of these when the rigid cervix was cut, delivery was prompt and spontaneous and her next delivery was easy. In all of these cases the perineum was cut or torn, but the prolapse did not recur. As a result of his experience, he is convinced that no abdominal operation is necessary for the cure of prolapse and since the parametria may be united in the midline without removal of the uterus, hysterectomy is unnecessary but should be reserved for those patients in whom the uterus is diseased.

In discussing the mechanics of the operation, Frank[7a] is of the opinion that the amount of shortening obtained by amputation of the cervix and suturing the parametria together does not account for the resulting fixation of the cervical tissues. He believes that the favorable result is obtained by condensation and shrinking of the parametrial elastic and connective tissues due to the aseptic trauma occasioned by the operation and resembling to some degree the fixation noted after infection of the parametria, the sole difference is that the scars obtained after the operation are resilient and entirely painless, while the opposite results after inflammation. In his experience the morbidity of the operation has been slight and there has been no mortality. His series includes 60 cases of first-degree prolapse, 30 cases of second degree, 14 cases of third degree and 3 cases of prolapse of the cervical stump, and in the entire series there was only 1 recurrence. He feels that the operation fulfills the requirements of a readily learned operative technique, applicable to a wide range of conditions, which

has proved more satisfactory than vaginal hysterectomy and avoids an abdominal incision with its possible sequelæ.

Interposition Operation. The operation known as the interposition procedure, with which the names of Watkins, Wertheim and Schauta are associated, consists of elevation of the bladder from the vaginal approach and supporting it by placing the fundus of the uterus between it and the vagina. By this means the uterus is interposed between the bladder and vagina and acts as a permanent pessary of autogenous tissue. It is an operation which is usually easy to perform and if used only in properly selected cases gives excellent results. The indications for the operation which are generally accepted are that the patient should be past the menopause with a large cystocele as the chief complaint, the uterus should be neither too large nor too small to act as an efficient vaginal plug and the uterosacral ligaments should be strong enough to hold the cervix well up in the pelvis. Many gynecologists disregard one or more of these factors, and for that reason obtain inferior results with the operation. With an experience of over 500 cases, Rongy, Tamis and Gordon[16] are well satisfied with their results and have extended the field for the operation by performing sterilization as a part of the procedure in those women who have not reached the menopause but have had enough children to suit their desire. They admit that there is a temporary disturbance of bladder function after the operation but this soon corrects itself as the bladder adjusts itself to its new position. They believe that no other operation corrects the displaced organs and cures the pelvic ptosis as does this one and at the same time preserving function so far as menstruation is concerned. They state that the operation is successful because fixed structures are used for support. The uterus acts as a shelf to hold the bladder and is elevated in the pelvis by being tipped forward.

A very interesting report has been made by Baer, Reis and Laemle[3] of two series of cases of over 200 patients in each series. In the first group the interposition operation was used as the operation of choice, and in order to see if results would be improved vaginal hysterectomy was employed in the second group as the preferable operation. In both series the patients were operated upon by the same group of gynecologists and it may be assumed that they were equally competent to perform either operation. They found that the interposition operation was completely successful in nearly 90% of the cases, whereas vaginal hysterectomy, to which they turned in order to improve their results, was successful in only 70%. As a result of this comparative study, it is their intention to again avail themselves of the interposition operation as a cure for prolapse of the uterus whenever the conditions for its selection are met. Vaginal hysterectomy will be used by them only in those cases of prolapse in which the uterine disease calls for hysterectomy. In women in whom childbearing is to be conserved they use the Manchester operation for prolapse of the first and second degree, while in third-degree prolapse they employ vaginal plastic reconstruction combined with a ventrosuspension.

A study of the sequelæ after the interposition operation has been made by Dannreuther,[6] which should be most interesting to any gynecologist who performs this operation. A number of patients complained of the onset of bladder annoyances long after their dis-

charge from the hospital and were found to be suffering from chronic trigonitis. Cystoscopic examination discloses an elevation and marked congestion of the trigone, with small depressions on either side, suggesting that the operator neglected to mobilize the bladder sufficiently in a lateral direction before pulling the uterus forward. He had 3 patients who complained of marked frequency of urination with tenesmus in whom vesical calculi were found. One had calculi in each of two lateral depressions of the bladder, another had a stone in a large posterior pocket behind the underlying uterine body, and the third had multiple concretions in both lateral and posterior areas. In all cases the urine was extremely turbid and loaded with colon bacilli. Vesical calculi are quite rare in the female since drainage is usually excellent, but in these cases the operators not only failed to mobilize the bladder sufficiently but 2 of them had also sutured the cut edge of the uterovesical fold of peritoneum too far back on the posterior surface of the uterus, thus fixing the floor of the bladder at a level below that of the trigone and creating a posterior pocket which tends to harbor residual urine with the later development of stones. In passing, it might be mentioned that the Reviewer has omitted this step of the operation for years with no adverse results and no pocket formation.

Incontinence of urine may be a symptom before operation and cured by it or the lack of control may persist after operation. The relief of this disturbance can almost be assured by preceding the major steps of the operation with a Kelly plication of the vesical sphincter. Since pregnancy is a highly undesirable sequel, he strongly urges against performing the operation in the childbearing woman. If, however, the operation is done combined with a bilateral tubal resection, as advised by some operators, it is important to do a thorough curettage in order to remove a possible attached fertilized ovum.

He has noted three types of postoperative vaginal protrusion, coming on as early as 10 months or as late as 7 years after operation. The first type is a reverse prolapse with bulging of the vaginal wall covering the overlying fundus. The descent of the uterus is exaggerated when the patient strains and it seems to be trying to dive "head first" out of the vagina. This is due to the fact that the fundus was not firmly fixed by stitching the cornu on each side to the periosteum under the pubic arch. The second type is that in which there is really a recurrence of the prolapse, the uterus breaking away from the vaginal wall as a result of defective suturing. The third type is an apparent postoperative bulging of the vaginal mucosa when insufficient tissue has been resected laterally in trimming the flaps. All of these defects are a source of discomfort to the patient and create the impression of an operative failure. Three patients who had been subjected to interposition operations later sought relief from severe menorrhagia due to fibroid tumors of the uterus. Such cases are a further argument against the use of the operation in women who have not reached the menopause. The development of new fibroid tumors is certainly uncommon after menstruation ceases, whereas the activation and enlargement of small intramural nodules is not unusual at any time before then. When fibroids are present at the time of operation, he believes that hysterectomy is always preferable to the interposition operation.

In order to overcome the weakness of the interposition operation in

cases where the uterosacral ligaments are overstretched, Chaffin[5] has described an operation which he terms a "vaginal subtotal." If the uterosacral ligaments are not strong, although the bladder will be retained by the operation, the uterus will slide down under the bladder at a subsequent time. To overcome this possibility, he performs a subtotal hysterectomy by the vaginal route and places the remaining cervical stump under the mobilized bladder. He then anchors the round and broad ligaments into a scarified area of the posterior vaginal wall just below the stump of the uterus, thus suspending the stump by structures which simulate the action of the uterosacral ligaments. He has performed the operation in more than 50 cases with entire satisfaction.

Vaginal Hysterectomy. In advocating vaginal hysterectomy for the cure of prolapse, Goff[8] states that the uterus is maintained at a normal level in the pelvis by the visceral part of the fascia endopelvina, especially by those parts of the fascia which are termed the transverse cervical or cardinal ligaments. The basic cause of prolapse is either a congenital defect in or an injury to these ligaments; therefore a successful operation for prolapse must be based on a shortening of these ligaments. He believes that the advantages of vaginal hysterectomy over other forms of operative correction are: 1, it facilitates the shortening of the cardinal ligaments; 2, it facilitates the correction of the abnormalities of the pouch of Douglas; 3, it removes a uterus which is either useless or abnormal in over 80% of the cases; and, 4, it removes the future possibility of neoplastic disease of the uterus. The operation should be used only in patients past the menopause whose physical condition warrants a major surgical procedure and in younger women who have the more marked degrees of prolapse or prolapse associated with pathologic lesions in the uterus. By employing the Bissell type of vaginal hysterectomy he has successfully treated prolapse of the uterus in 98% of his cases.

Colpocleisis. The word "colpocleisis" means occlusion of the vagina and as practised surgically by the gynecologist it may be subdivided into two types, namely, partial occlusion as typified by the LeFort operation and total occlusion which is also called colpectomy. In the opinion of Simon[19] this operation has fallen into an undeserved oblivion in this country largely because it involves the complete anatomic and physiologic loss of the vagina. However, simplicity of performance, safety, uniformly good results and applicability to conditions not amenable to any of the reconstructive types of operation insure for it a permanent place among useful operations. Prolapse in the aged constitutes the most frequent indication for this procedure since it may be done in a short time under local anesthesia. There can be little objection to the loss of the vagina after the age of 70, while the menopause would probably mark the limit below which the operation would be contraindicated. Between these limits he believes that the selection of the operation would depend on the social status of the patient, her physical condition, the feasibility of performing some more conservative procedure, and finally, but not of least importance, on the consent of the patient herself after all aspects of the operation have been explained to her. The operation is also indicated in the treatment of prolapse of the vagina or vaginal hernia after hysterectomy,

either of the abdominal or vaginal type, recurrences after the interposition operation, and in the treatment of prolapse in nulliparous women.

Subtotal colpectomy, or the LeFort operation, was devised for the treatment of prolapse by vaginal occlusion without removal of the uterus. It provides for the drainage of the secretions of the uterus and cervix by the formation of a transverse cavity beneath the cervix, which communicates at each end with two laterally placed canals leading to the surface at the vaginal orifice. Such provision for permanent drainage is essential in all cases in which the uterus is left in place, even after the menopause. In the LeFort operation two rectangular areas, one on the anterior and one directly opposite on the posterior wall of the vagina, are completely denuded of mucosa. The upper limit of each rectangle should not extend beyond a point 2 cm. below the cervix; the lower limit posteriorly corresponds to the mucocutaneous junction; anteriorly it extends nearly to the urethral opening. The width of each rectangle should be such that the mucosa remaining on each side will form a canal about 1 cm. in diameter. After bleeding is controlled the denuded rectangles are then accurately apposed and sutured together from above downward with interrupted catgut stitches. A perineal repair when indicated should be performed as part of the operation. The experience of Adair and DaSef[1] with this operation has been very satisfactory, especially since 64% of the patients on whom they performed it had some condition contraindicating extensive operative procedure. They emphasize that the prolapse should be capable of reduction, erosions of the cervix and vaginitis should be eliminated by suitable treatment, the corpus and adnexa should be free from disease, the sexual life of the patient should no longer be of importance and the consent of the husband should be obtained. In reviewing the literature they collected 260 cases with satisfactory results in 86%. In those cases in which there were recurrences the causes were almost always the same, either failure to make the lateral channels small enough to prevent recurrence of the prolapse through the side canals, or failure of the sutures to hold, with resulting partial separation of approximated surfaces. Deaths have usually been due to thrombosis and cardiovascular disease. There is one major objection to the operation and that is that it prevents any later examination of the cervix. For this reason it is necessary that the cervix and the uterus should present no abnormality at the time of operation and if any suspicious lesion is present, a vaginal hysterectomy should be done. However, the incidence of uterine carcinoma in women with atrophied uteri is not great and they have found only one report of carcinoma following the operation. In order to overcome the necessary termination of sex life which the classical LeFort operation entails, and interesting modification has been devised by Goodall and Power[9] in which the denudations of the vaginal walls are made in the shape of triangles in the upper part of the vagina, the apices of the triangles pointing toward the vaginal outlet. The denudation usually involves only the upper third of the vagina so that when they are apposed there remains a single vagina in the lower two-thirds with a double vagina in the upper part. The apposition of the upper anterior and posterior vaginal walls prevents prolapse while the single vagina below permits sexual intercourse.

At the Mayo Clinic, according to Masson and Knepper,[12] both partial and complete colpectomy are used with very satisfactory results, the average age of the patients being 58.5 years. The exposure and irritation of the vaginal mucous membrane had caused an unnatural dryness and thickening which usually had caused the cessation of sexual relations before the patients sought medical advice. In performing complete colpectomy, after removal of the uterus by vaginal hysterectomy, the broad ligaments are approximated in the median line and firmly fixed well up under the pubic arch. They are then sutured posteriorly to the levator ani muscles which have been thoroughly freed and sutured in the median line as in an ordinary perineorrhaphy. In this manner a strong pelvic floor is reconstructed and the closure of the rest of the vagina is easily accomplished, after removal of all mucous membrane, by interrupted transverse sutures, some of which are silkworm gut, and are left in place for 12 to 14 days. It is advisable to provide for drainage by inserting a small tube. If an enterocele is present the peritoneal sac should be removed before commencing the closure.

Prolapse After Hysterectomy. The occurrence of prolapse of the vaginal walls some time after the performance of a hysterectomy is a most unpleasant sequel. While in many instances it can probably be corrected by a colpocleisis as previously described, if it occurs in a sexually active woman, some other method of treatment must be considered. Brady[4] has met this difficult situation in 1 instance by making a lower midline abdominal incision and opening the fascia and peritoneum only in the upper part of this incision. A Cameron light introduced into the vagina pushes the vaginal vault upward so that it is easily recognized from within the abdomen. Three medium-sized braided silk sutures are introduced from above into the top of the vaginal vault and are then passed through the peritoneum and fascia of the lower part of the wound and tied on the external aspect of the fascia, thus fixing the vagina to the anterior abdominal wall. The relaxed round ligaments were reefed and sutured to the vagina, preventing the bladder from prolapsing laterally. A perineorrhaphy completed the operation.

Ward[20] successfully treated a case of this type, the patient having been followed for 4 years after operation. The operation he employed consisted of a reconstruction of the round ligaments of the uterus by the use of preserved ox fascia lata. After suturing the fascia lata to the vault of the vagina from within the abdomen, these newly made ligaments were continued anteriorly under the peritoneum of the bladder to give added support to that organ. The new round ligaments were entirely extraperitoneal so that there was no danger of intestinal obstruction from free bands within the peritoneal cavity.

Intestinal Obstruction Complicating Prolapse. Although prolapse is often complicated by an enterocele, incarceration and obstruction of the contained bowel is rare. The case reported by Frank[7b] was a 42-year-old multipara who had had a reducible prolapse for 1 year. Two weeks before admission the prolapse became irreducible and for 2 days no flatus was expelled. On admission she presented a huge prolapse ulcerated in several places, which could not be reduced after

considerable trial. On opening the abdomen it was noted that the prolapse contained both large and small bowel which could not be reduced. After decompression of the small bowel by needle puncture, the bowel could be replaced into the abdominal cavity and then after considerable pressure from below the large prolapse was inverted and the abdomen closed. Four laparotomy pads were packed into the vagina to prevent recurrence of the prolapse. The patient had a rather stormy convalescence due to various complications but 8 weeks later it was possible to perform a parametrial fixation for the cure of the prolapse with a successful result when seen after 14 months. One of the reasons that irreducibility of prolapse is rarely encountered, according to Frank, is that unless an extremely sluggish and unintelligent patient suffers from this trouble, the symptoms are so acute and violent that immediate help is sought. In the early stages before stasis and edema have occurred, reduction should always be possible.

Intestinal obstruction following round ligament operations has been recognized as a possibility for many years, but since it rarely occurs we are prone to think lightly of it. A personal experience with 2 cases within 1 year has vividly brought to my mind the seriousness of this complication. C. C. Norris has also seen 2 cases and a third case following shortening of the uterosacral ligaments. These cases, which were reported by Michael[14] were both instances in which the small bowel became strangulated between the anterior abdominal wall and the round ligament which had been sutured to it, leaving a lateral pocket. It is important that such a condition should be strongly considered in any patient who presents symptoms of ileus following a previous uterine suspension. Since this experience, it has been our practice to close the space between the round ligament and the abdominal wall on each side in all cases in which the Olshausen type of operation is done, feeling that the slight additional operating time is well spent. That such obstructions do not only occur after this type of operation is shown by the report of Arnold.[2] In his case a loop of ileum became obstructed through the broad ligament at the site where the round ligament was pulled through in the performance of a Baldy-Webster operation 9 years previously.

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DERMATOLOGY AND SYPHILOLOGY.

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LYMPHOGRANULOMA VENEREUM.

LYMPHOGRANULOMA venereum is especially deserving of consideration as an excellent example of both the speed and the completeness with which modern investigative methods can organize from scattered beginnings the completely evaluated picture of a disease entity. Within a quarter century, climatic bubo or so-called suppurative inguinal adenitis of unknown etiology in males (Trousseau,[121] 1865; Godding,[28] 1896); Nicolas-Favre's disease,[18] subacute localized and suppurative lymphogranulomatosis in the inguinal region, and the lymphogranuloma inguinale of the years immediately preceding the World War, have all been swept into one category of what appears to be a disease entity. The venereal origin, although suspected for many years, was finally proven by Phylactos[85] in 1922. Gamna,[25] in 1923, had reproduced the inguinal lymphatic form in guinea-pigs. The successful transmission (1930) of the infection to other animals by Hellerström and Wassén[44] with confirmation by Levaditi and his coworkers[62,63a,b,c,64,65] (mouse-brain inoculation) and by Findlay[21a] established experimentally the etiologic unity of the disease. Frei's introduction from Jadassohn's Clinic, in 1925,[23a,24] of the intracutaneous test made possible the inclusion of esthiomène and poradenitis and finally of rectal stricture (Jersild[50a,b]) with the clinical and pathologic picture of lymphogranuloma venereum. From the literature between 1930 and 1936, it is now possible to collect (Bacon[3b]) 3977 reported cases which conform to the newer conception of the disease entity, even though it is not wise as yet to speak of them all as absolutely proved. This rapidly developing knowledge has inevitably resulted in a confusion of nomenclature for which no immediate resolution, unless by international agreement, seems in sight. The name for the disease officially adopted by the American Medical Association is "lymphogranuloma venereum." Among the chief summaries of the subject in the literature are those by Hellerström,[43] DeWolf and Van Cleve,[17] Sulzberger and Wise,[114] Wolf and Sulzberger,[126] Cole,[11] Stannus,[112a,b] Martin and Bacon,[73] J. C. Levaditi[67] (experimental), Thompson,[119] Löhe and Schlossberger[70] (complete clini-

cal and experimental), Bloom,[7b] W. Frei,[23c] and Jones and Rome.[51] The chief workers and active study centers of the world include Hellerström (Stockholm), Levaditi (Paris), Findlay (London), Stannus (London), Miyagawa (Tokyo). Wilhelm Frei who originated the cutaneous test while in Breslau is now an expatriate, working in New York City (Montefiore Hospital). Nicolas and Favre (Lyons, France) are still active in the field. The work of European investigators was introduced to this country by Sulzberger (New York), and popularized by Cole (Cleveland). Grace and Suskind[32,33a,b,c,d] have worked actively with mouse brain antigen. Strauss and Howard[46,113a,b,c] have written extensively on the Frei test; extended American work on anorectal granuloma has been done by Martin[72] and Bacon[73] (Philadelphia), Cole[11], Mathewson[74] and Bloom.[7a] Some of the most important recent investigative work, particularly on the culture of the virus, is that of Tamura[115a,b] (Cincinnati). W. E. Coutts (Santiago, Chile) has been the chief South American student.

Work on the Virus. The priority and validity of the earliest work on the virus, including that of Gamna (1923) and Favre (1924) is discounted by Findlay, who credits Gay-Prieto[26] with the earliest recognition of small cytoplasmic granules in the cells of the inguinal bubo, as also described by Findlay[21a] in 1933. The work of Miyagawa and his group[78a,b] seems supportive of the contention that these granules actually represent the infective agent. They are uniformly present in the lesions of lymphogranuloma venereum in man, in the brains of infected mice and monkeys, and in the experimental buboes of guinea-pigs. The presence of similar granules in the chorio-allantoic membrane of the developing chick embryo infected with lymphogranuloma venereum and in the cells of the rabbit's cornea grown in tissue culture is also regarded as confirmatory. Tamura[115a,b] has demonstrated the presence of granules in the tissue containing Maitland-Tyrode medium cultures of the virus. The dimensions of the virus as measured by various observers are similar to those of the vaccinia virus, 0.24 μ to 0.33 μ in diameter, easily passing through such filters as Chamberland L_2 and L_3 Berkefeld and Seitz.[78a] An antiserum prepared in rabbits, from which the elementary corpuscles have been removed by differential centrifugation contains no viricidal immune bodies, while an antiserum prepared from relatively concentrated suspensions of elementary bodies does contain viricidal immune bodies (Findlay[21b]). Tasaki,[116a] Grace and Suskind,[33d] Coles,[12] Herzberg and Koblmüller[45] have all confirmed the virus work of the Japanese investigators. Landmarks in work on the virus have included Levaditi's transmission of the infection to the mouse brain,[64] the demonstration of the virus in the pus of the inguinal bubo (Hellerström and Wassén,[44] Cohn and Kleeberg[10] and others) and the demonstration by many workers of the presence of the virus in all the recognized lesions of the disease (hypertrophic and stenotic inflammatory rectal lesions,[90,120] vulvar esthiomènes[55a,b] and primary genital lesions[71]). Beginning with the transmission of the infection to monkeys by Hellerström and Wassén,[44] the infectibility of many animals and especially of rodents has been demonstrated. The horse, rat, chicken and frog have thus far proved refractory.[67] In the monkey, the virus does not remain localized in the nervous tissues, but passes the blood-nervous tissue barrier and is carried by the lymph and

leukocytes to regions of the body rich in histiocytic cells. In the guinea-pig, the infection seems limited to the local primary lesion and its regional lymph nodes.

In addition to the demonstration of the virus from all recognized lesions of the disease, it has been shown to be present in the spinal fluid by von Haam, and R. D'Aunoy[38] and in the secretions of a case of acute conjunctivitis.[60] Of even more significance is the statement of P. Ravaut,[67] that the virus was obtainable from the intact vaginal mucous membrane of a patient with enlarged inguinal lymph nodes, and that of Caminopetros,[8] who purports to have found the virus present in the vagina at least 18 months after infection. It has also been identified in non-bacterial urethral and vaginal discharges. There seems reason to believe (von Haam and D'Aunoy) that the virus of the disease exists in human beings as long as the lesions are present.

Löhe and Schlossberger's[70] valuable review demonstrates clearly the shortcomings of our immunologic knowledge concerning the infective agent. They find that successive animal passage heightens virulence, but as yet, nothing in the way of vaccination experiments with attenuated virus or any immunizing prophylaxis seems to have developed. Suggestions of tropism and elective localization include the observations on migration of the virus to centers of histiocytic activity above mentioned and the clinically recognized predilection for the localization and extent of the process in the lymphatic system. This lymphotropism, in fact, is responsible for the important differentiations in types of involvement observed in clinical practice.

Epidemiology. Lymphogranuloma venereum, so far as present knowledge indicates, is distinctly a venereal disease. Non-venereal and extragenital infections have thus far been reported almost entirely among physicians, research workers, nurses, and children accidentally inoculated by such conveyors of the virus as enema tips. H. Levy's report[68] disclosed only 9 cases in children throughout the entire literature, and an additional one reported by the author (see also Elitzak and Kornblith[20]). A characteristic early transitory vaginal discharge with urethritis in children accompanied by inguinal adenitis was the chief suspicion-arousing characteristic. Nicolau[82] believes the transmission to the child in his case was by way of the bed-clothing. Finger inoculations have occurred in workers with the disease, with lymphatic extension *via* the axilla. Tongue and tonsillar primary and secondary lesions have been recorded, usually ascribed to perversion. Löhe and Schlossberger[70] cite Walter as having described a case and themselves report an instance in which they believe evidence of congenital transmission of the disease is disclosed. Studies in epidemiology must take into account the fact that the virus is active at room temperature for 24 to 48 hours, loses its virulence at a temperature of 46° C. for 30 minutes, is killed in 10 minutes at 56°, but is unaffected by freezing temperatures for 1 day. It remains active after drying for 30 days, and may transmit the disease in dilutions as great as 1 to 10,000.[78b] The extremely important question of asymptomatic carriers of the disease deserves further study. The identification in routine testing of persons who have positive Frei tests with no history of lesions for years; the occurrence of an infective urethritis with no other manifestations, and of an apparently normal condition of the vaginal mucosa accompanied

by the presence of the virus, suggest the public health importance of this group of phenomena.

Most of the evidence that has been collected relative to the distribution of the disease through the population has been based on studies of clinic patients and upon those who are sexually promiscuous or actually engaged in prostitution. Whether the figures available therefore represent sound conclusions on the distribution of the disease throughout the population and in medical practice may well be doubted. Gray, Hunt, Wheeler and Blache[34] studied the prevalence of the disease in St. Louis, and found the number of positive Frei tests in whites to be 3.4%; in colored patients, 40%; white prostitutes were positive in 4.4%; colored prostitutes in 47.7% of cases. Not more than 40% of the cases identified were active. De Wolf and Van Cleve, reporting from Cleveland, found 58 positive Frei reactions among 1010 persons treated. Haim and Mathewson,[40] studying the incidence in San Francisco (1937) found 60 proved cases on the records of the Marine Hospital; 46 proved cases were observed in the San Francisco General Hospital. Seven hundred adults were surveyed by means of Frei test, with 2.7% positive and 2.7% doubtful in the San Francisco General Hospital and 8.9% positive, 3.2% doubtful in the Marine Hospital. Of the latter group, one-third were venereal disease cases. Tasaki and Kamimura,[117] examining prostitutes in Harbin and Mukden (995 cases in all) found 12.8% of the Japanese, 23.4% of the Koreans, and 27.2% of the Chinese prostitutes with positive Frei tests. Those without clinical signs constituted approximately 80% of the group. Goldblatt[30] found that 32% of the prisoners quarantined for venereal diseases in the Cincinnati workhouse gave positive Frei tests when tested with several antigens. Clyne,[9] at Fort Sam Houston, Texas, during a 13 months' period, recognized 48 cases of lymphogranuloma venereum, and, comparing the incidence rate with that of other venereal diseases, found that it constituted 4.1% of admissions (that is, 48 cases in 1158 of syphilis, gonorrhea, chancroid and lymphogranuloma venereum). This is approximately one-fourth the incidence of chancroid. Simon and Bralez[111] (Saint-Lazare Hospital), in 412 entries of unsuspected individuals on a hospital service, found lymphogranuloma venereum as judged by the Frei test, in 4.1% of cases. Hanschell,[41] at the Seamen's Hospital, London, found 130 cases among 17,900 admissions for other genito-infectious diseases. The comparative rarity of the disease in Great Britain has been mentioned by Stannus.[112a]

An examination of the available reported material tends to indicate that neither sex nor race influences the incidence or distribution of the disease. It appeared that the asserted greater prevalence of the infection in the negro is more probably due to sexual promiscuity and high rate of exposure than to any intrinsic susceptibility on the part of the negro individual. So far as age incidence is concerned, the statistics collected by Hashimoto and others[42] tend to indicate that the peak of incidence corresponds to the peak of sexual activity, and contains no element of age, immunity or predisposition (see also A. Sézary and others[107]).

The geographic distribution of the disease has shown variations, dependent on the source of the material, more obviously than any other consideration. It is obviously no longer to be regarded as a seaport

disease, and the distribution of the some 4000 reported cases indicates that interest and location in a region where sexual exposure runs high in the population gives an impression of prevalence. Nonetheless, an observer of Frei's experience has stated that the disease appears to have endemic centers at times of maximum prevalence which do not necessarily conform to those of other venereal infections. Epidemic and endemic foci are occasionally dependent on single sources of infection, as in the case of the Greek island reported by Serefis,[96] in which practically the entire population was affected, following the introduction of the disease by a single infected prostitute.

Public Health Considerations. Frei[23c] summarizes the situation with reference to public health control (1938) by a comparison with syphilis, in which he points out that only one laboratory diagnostic method of lymphogranuloma venereum exists as compared with two for syphilis, and that the supply of diagnostic material is thus far limited though improvable with the development of new methods (including possibly mouse-brain antigen). No method of treatment of lymphogranuloma venereum thus far proposed has the immediate disinfectant action of the arsenicals in syphilis. So far as we have been able to ascertain from the available literature, no provisions are contained in the laws of the states in this country relative to reporting, and the availability of antigen for diagnosis is practically entirely that of private sources of supply. Sweden, in 1934, was the first country to take national cognizance of the disease as a public health problem, though the Office International d'Hygiene Publique[83] has thus far made no recommendations, but has conducted an international investigation. As in the case of syphilis, it should be pointed out that the woman is apparently the uncontrollable and in many respects the most important part of the resevoir of infection. Since vaginal secretions can be infectious apparently in the absence of any open lesion,[8,67] and since the inoculative stages in the woman usually involve the posterior lip of the cervix and the deeper portions of the posterior wall of the vagina, it is obvious that clinical detection of the disease in this sex, especially will lag far behind its public health desirability. Routine Frei test examination of prostitutes has the serious defect that positive tests are obtained in persons in whom the disease has definitely reached the inactive and presumably non-transmissible stage.

Since the disease is more definitely a genital infection than syphilis and the area of infection more distinctly confined to the mucosal surfaces, it would seem that mechanical prophylaxis, if effectively carried out, is probably as useful in prevention as anything at present available.

The Clinical Picture. It is not the purpose of this review to detail the clinical course of lymphogranuloma venereum, but the following statement briefly summarizes the essential facts. A primary sore or lesion usually appears from 2 to 5 days after the infective coitus and in the male is most commonly observed on the coronal sulcus, but may appear on the glans, the prepuce, or in the urethra. There may also be a balanitis. In females, while the inoculatory lesion may occur on any part of the external genitalia, the usual site, as already mentioned, is the posterior vaginal wall, posterior lip of the cervix, or in the neighborhood of the fourchette. The lesion is a small herpetiform vesicle or ulcer, circular or lenticular, sometimes multiple, with clean-

cut edges surrounded by a reddened zone but with no induration or infiltration. The base of the ulcer is whitish gray and forms a small rounded hollow of pin-head size. The lesion is asymptomatic, heals spontaneously and is often missed both by the patient and physician. Hashimoto and others[42] found the primary lesion to consist of a small erosion in 56%, an infiltrated papule in 39%, and a herpetic lesion in 5%. The incubation period in their series, it should be noted, can be as long as 5 weeks (3.8%) but was 1 week or less in 70% (see also Sézary and Friedmann[103]). The lymphotrophism of the virus leads to the development of a bubo in the drainage area of the primary lesion, the incubation period for this manifestation from the time of infection ranging from 4 days to more than a hundred, and being most frequently 10 to 29 days (48%). The early impression that lymphogranuloma venereum was exclusively a disease of males, as well as the failure to identify the vulvar and anorectal granulomas with lymphogranuloma venereum was a consequence of the lymphatic distribution of the virus. When the primary lesion occurs in the inguinal lymphatic drainage area, whether in male or female, inguinal buboes and esthiomène are the prevailing manifestations. When inoculation occurs in the vagina or upon the cervix, direct extension of the infection through the rectovaginal septum leads to the syndrome of anorectal lymphogranuloma. The bubo localization is prevailingly inguinal and iliac (more frequently the latter) and more frequently unilateral than bilateral (Kitchevatz and Alcalay.[54] Occasional inguinal, femoral, and inguino-femoral and iliac involvements occur. Hashimoto and others[42] found the inguino-iliac and inguino-iliac-femoral to represent 58.4%, the inguinal 36.4%, and the inguino-femoral 5.2% of the localizations. From the secondary adenopathy at first recognized by the patient through a sensation of stiffness and aching followed by swelling, the process may come to an end, or after retrogression, may light up again. It usually extends, however, until all the glands of the group are usually involved, with considerable periadenitis, the mass becoming fixed and adherent to the skin which is of a rather characteristic purplish color (Stannus[112b]). The iliac glands may form masses as large as a child's head. Inflammatory changes continue with softening, and the formation of abscesses and fistulæ from which a characteristically thick viscid, tenacious opalescent yellowish-white pus exudes and in which no organisms can be demonstrated by the usual cultural methods. In a period usually extending from 2 months to 2 years, the glandular swelling subsides, drainage is complete and healing takes place. If the destruction of glands and surrounding tissue is widespread, secondary elephantiasis of the leg and pudenda may follow, or there may be a complicating phlebitis. Extensive and critical suppuration of the lumbar glands, extensive destruction of the psoas muscle and extension of the infection to articular surfaces and to the kidney and adrenals of the involved side have all been observed.

The constitutional symptomatology, while not highly specific, adds lymphogranuloma venereum to the group of conditions to be considered in persons who present slight fever,[56,102] slight leukocytosis with mononucleosis,[9,48,57a] increased sedimentation rate,[57b,124] and alterations in blood lipids and proteins.[36,91,116,124,125] This last-mentioned change is regarded as of diagnostic significance by Jersild,[49] Howard, Eisenman

and Strauss.[47] After summarizing the observations of a number of investigators and their own work, Rosen, Rosenfeld, Bloom and Krasnow[92] support the diagnostic importance of the lipid-globulin relationship by observations on 116 cases. Hyperglobulinemia occurred in 100% of their cases, and was most marked in the late stage (rectal stricture and esthiomène). They rate this hyperglobulinemia then as a valuable diagnostic lead. The serum lipids were uniformly decreased. In chancroid, for example, there may be an increased globulin content but there is no decrease in the lipids. These observers found that treatment of the lymphogranuloma venereum brought the lipid values to normal but left the globulin unchanged. Gutman and Wise,[37] reporting on the positive formolgel reaction associated with hyperglobulinemia in lymphogranuloma venereum, point out that the hyperglobulinemia may be responsible for other somewhat erratic or abnormal findings in the blood of patients with this disease. For example, the high sedimentation rate, often greatly in excess of the level consistent with the degree of obviously active infection; the falsely positive and repeatedly anticomplementary Wassermann reactions reported in the literature,[114] may be regarded as phenomena attendant upon the hyperglobulinemia.

That lymphogranuloma venereum is a systemic infection, is borne out by the occasional examples of meningitic and meningo-encephalitic involvement.[15] Rajam,[89] in reporting a fatal case, summarizes the spinal fluid findings in the reported examples, including Midana and Vercellino's examination[77] of 11 cases, in which all except 2 were normal. The abnormalities reported by this author and by Kitagawa[53] are apparently not specific or characteristic (see also Clyne,[9] Mollaret and Vieuchange[79]). It will be recalled, however, that the virus has been recovered from the spinal fluid.[38]

Jones and Rome[51] have collected the literature of systemic manifestations, including pulmonary involvement and ocular localizations with regional adenopathy, tonsillar ulcers, ulcerative angina, arthritis at points distant from the site of initial involvement, occasionally simulating rheumatic fever or purulent arthritis. The dermatologic manifestations include erythema multiforme, erythema nodosum, scarlatiniform eruptions, papular lesions, ulcers, and giant keloid formation. Particular interest attaches to the characteristic lymphogranulomatids reported by Saenz[94] and by Goldberg and Fondé[29] which are indicative, theoretically at least of vascular dissemination and allergic characteristics in the disease.

The "late" lesions of lymphogranuloma venereum are unfortunately seen in the large majority of cases only after extensive scarring has taken place, and are, therefore, to a considerable degree, residua rather than active and treatable infectious lesions. The relatively unsatisfactory drainage of the anorectal type of infection, according to Stannus[112b] prevents rapid evacuation of the virus from the infected locality and leads to the extensive destructive and deforming lesions of esthiomène and anorectal lymphogranuloma.[93] Rosser, in whose opinion Collier Martin concurs,[72] pointed out the importance of the keloid or fibroplastic diathesis in the negro in producing the extraordinary hypertrophic and elephantiasic pictures, particularly in the negro female, to which the latter author once applied the term "negromata." Finkel-

stein[22] and Stannus[112b] and others have all directed attention to the low position of the strictures in anorectal granuloma, characteristically recognized in the Roentgen ray at 2 and 6 cm. above the anal orifice. Finkelstein also calls attention to the roentgenologic picture of the tubular arrangement of the lesion with indistensible walls and preservation of the mucosal pattern, and perirectal sinus visualization. The special student of the rectal pathology and clinical manifestations should read the papers by Cole,[11] by Vander Veer, Cormia and Ullery,[122] by Mathewson,[74] by Bloom,[7a] and by Bensaude and Lambling,[5] and Stannus.[112]

The Frei Test and Other Diagnostic Procedures. Inasmuch as the Frei cutaneous test is the principal diagnostic resort at the present time, the only procedure which is applicable to surveys and routine testing and the most important diagnostic or confirmatory evidence available in the early stages of the disease, some description of special technical detail is worthwhile. Two main sources of antigen, so-called, are recognized: the pus from the inguinal bubo and emulsion of the brains of intracerebrally infected mice. With reference to the Frei antigen, the most recent specifications of the author[23c] of the test may be quoted:

"The material needed consists of the diluted and sterilized pus of proved, non-ruptured pure buboes of venereal lymphogranuloma. One-tenth cubic centimeter is injected intracutaneously and the reaction is read after two days. In a positive case, one finds an inflammatory papule of at least 0.5 cm. in diameter, often with peripheral erythema and sometimes with a central pustule. In negative cases there is none, or very little reaction after two days. Only tested vaccines corresponding to these conditions should be available for general use. On account of the possibility of generalized or focal reactions, it is not advisable to make the test in hyperacute stages of the disease or in cases in which suppuration occurs near the peritoneum."

A positive reaction does not prove that the disease still exists, because the power to react to the test remains in healed cases for decades. A negative reaction in cases of venereal lymphogranuloma occurs in the earliest stage of the bubo, and in some cases in which there is transitory or constant anergy. In cases of anergy a positive result may be obtained by the so-called inverted test, in which the patient's sterilized pus is injected into the skin of a patient with proved lymphogranuloma venereum, producing a positive reaction, or the usual vaccine is injected intravenously instead of intracutaneously into the suspect, and if he has the disease, he may respond by a generalized febrile reaction. It may be said that the venereal lymphogranuloma cutaneous test results in about 95% of positive reactions when buboes have developed, and in about 90% when there is ulcerative elephantiasis. In discussing the sources of error in the use of his test, Frei[23b] has given unspecific inflammatory reaction resulting from the use of vaccines contaminated with living or dead bacteria as the chief source of trouble. "The danger of contamination is very great since the vaccine is prepared without any antiseptic and thus furnishes an excellent culture medium. For purposes of sterility one must therefore watch and control every little step in obtaining, preparing and using the vaccine. For example, I (Frei)

originally put the vaccine up in small vials and used them on several occasions. Later, to assure sterility, I replaced the vials by small ampoules, each containing sufficient vaccine for only one test. Here in America, I found in various places the old vial system, but with one difference; namely, that the vaccine is aspirated through the stopper, while I had to remove the stopper."

In a bacteriologic study of material prepared and supplied with rubber stoppers, Frei reached the conclusion that the use of a rubber stopper is a potentially fertile source of trouble from infection of the vaccine, especially where the general practitioner repeatedly punctures the cap under merely alcohol sterilization. In discussing the inverted test especially, when a similar technique is applied to other body fluids and discharges such as mucoid urethral secretions, spinal fluid, bowel secretion from ulcerative colitis[84a,b] and so forth, Frei believed that serious non-specific elements may enter into the interpretation. Sézary and Georges-Lévy[104] found most of the difficulties due to defective antigen, and Durel and Dreyfus[19] believe the quantity ordinarily used to be insufficient. They insist on 0.3 cc. as the optimum amount.

Frei has thus far refused to express himself on the use of mouse-brain antigen, on the ground of lack of experience. A controversy over the specificity of mouse-brain antigen has, however, developed among various observers, which is discussed by Grace[31] in recent correspondence. Grace insists upon the importance of the measurement of the papule produced by the antigen as the only reliable means of differentiating between non-specific reaction due to injected foreign tissue substance and reaction actually due to the presence of the virus. He states that mouse-brain antigen has been so standardized that 0.1 cc. intradermally in lymphogranulomatous subjects produces an erythematous papule not less than 7 mm. in diameter and usually from 7 to 10 mm. In 823 control tests, no papule larger than 6 mm. was produced, and in less than 6% only were the papules as large as 6 mm. The necessity for this type of accurate measurement of the papule size and the differentiation between specific and non-specific reactions based on such comparatively small differences has led Binkley and his associates[6] to believe that the test as performed with mouse-brain antigen is unreliable (see also Strauss and Howard[113b]). Favorable reports, however, have been published by von Haam and Hartwell,[39] Lichenstein and von Haam,[69] D'Aunoy and von Haam,[14] Bacon,[3a] and Bloom.[7b]

Melczer and Sipos[75] have experimented with a complement fixation test for lymphogranuloma venereum with 87.5% positive and 12.5% non-specific reactions. Midana,[76] on the other hand, was unable to obtain any positive complement fixation tests on 21 patients with lymphogranuloma venereum. Coutts and Ponce[13] have reported a method which gave 100 negative controls in the presence of highly syphilitic sera, and believe the method therefore to be highly specific for lymphogranuloma venereum. The blood serum changes which may be explanatory of anticomplementary and falsely positive blood Wassermann tests for syphilis in patients with lymphogranuloma venereum have been mentioned above.

Pund, Greenblatt and Huie[87] have discussed the usefulness of biopsy in the diagnosis of lymphogranuloma venereum from tissue. The histologic picture for those who desire to study this question has been

described by a number of authors, including Stannus,[112a] Thompson,[119] De Wolf and Van Cleve,[17] and Jones and Rome.[51] Frei believes that the microscopic study of sections offers some useful points in differentiation, of lymphogranuloma from other inflammatory and suppurative diseases, including tuberculosis.

Culture of the virus is still a purely laboratory method not yet available for diagnosis. Animal inoculation, however, has a limited value, especially the inoculation of mice, which develop an encephalitis following intracranial injection. This presents fairly characteristic histologic pictures, from which the virus may subsequently be obtained for test purposes.

Treatment of Lymphogranuloma Venereum. Any discussion of the relatively unsatisfactory treatment of this disease should be preceded by emphasis on the occurrence of spontaneous recovery. Its frequency is inferred from the large number of Frei test positives obtained in surveys in patients who no longer show any active clinical evidence of the disease. The treatment of the early manifestations of lymphogranuloma venereum includes local surgery and irradiation. Stannus[112b] states that in early cases of inguinal adenitis with only one or two glands involved, a minimum of periadenitis and the skin free, radical excision is often effective. On the other hand, any attempt to remove a large mass of matted glands and adherent tissue must be deprecated. Aseptic aspiration, repeated when necessary, as long as the skin is intact, is probably the wisest course. Negru[80] found that in non-purulent cases, Roentgen irradiation with massive doses of hard rays produced healing in at least 50% of the cases. In draining or granulating cases, irradiation is also useful, and promotes healing of the operative wound.

The drug therapy of lymphogranuloma venereum testifies by the multiplicity of remedies to non-specific and relatively unsatisfactory results. Local injections, as of glycerin, or xylol-iodoform, have little value. Iodine and iodide (Lugol's solution), 10 cc. in an equal quantity of saline, daily intravenously, or 10 cc. of a 10% solution of sodium iodide have been favorably reported. Copper ammonium sulphate, Solganal (a gold preparation), sodium salicylate intravenously, and by mouth, fever therapy, and non-specific vaccine and non-specific protein all have some good results to their credit. The most important drug in the treatment of the disease at present is unquestionably antimony, which, as potassium antimony tartrate, has probably had the most extended trial.[95] Lithium antimony thiomalate (anthiomaline) seems to have had the most favorable reports. Sézary and his associates,[98–101,106] Setien and Farinas,[97] Shaffer, Fondé and Goldberg[108] and others[1,81] have emphasized the striking symptomatic effects of this antimony compound and its relative freedom from toxic effects. All writers are said to report that 50 or 60% of cases show rapid improvement, 20 to 25% show a slow but good effect, and 20 to 25% remain unresponsive. It is notable that considerable relief can be obtained even in the anorectal syndrome. Sézary,[98–101,106] however, failed to note much benefit in such cases in which, of course, the proportion of scar to active process must be an important consideration. The drug is administered 2 or 3 times a week with an initial dose of 0.06 gm. and increments of 0.03 gm. until the rheumatoid pains typical of anti-

mony reaction appear. The dosage is then reduced until the pains are barely perceptible several hours following the injection. This dose is usually approximately 0.12 to 0.24 gm., but some patients may tolerate as much as 0.3 gm. A course totals 2 to 4 gm. of the drug (12 to 20 injections) with rest periods of 2 to 3 weeks before beginning the second or final course. Fuadin, another antimony preparation, is rated an effective drug by a number of observers, and definitely to be preferred to surgery as a means of shortening the course in most cases.

Shaffer and Arnold[109] treated 22 patients with lymphogranuloma venereum by the use of sulphanilamide, with 4 seemingly complete recoveries, 11 marked improvements. Their study of the German and French literature[50,66] confirms this favorable experience (see also Qualls[88]). Gjurić[27] obtained his best results with fuadin and prontosil (see also Bär[4]). Shropshear[110] had excellent results in the ano-rectal syndrome.

The biological treatment of lymphogranuloma venereum includes first of all the use of the Frei antigen ("vaccine") derived both from human and monkey[16,61] and from mouse-brain sources, and administered both intradermally and intravenously. Wien and Perlstein[123] have reported on 200 patients in a series of 500 treated by this method with the conclusion that conservative treatment by the intradermal injection of Frei antigen is more effective and less associated with destruction and disability than any other procedure. Prehn[86] gives a series of at least 8 injections, 1 every other day intradermally, close to the site of the lymphadenitis with very favorable effects. Anderson and Harmos[2] treated 48 cases with sterile potent Frei antigen, diluted 4 times (1 to 4 or 1 to 28 dilution of the heat-treated pus in physiologic salt solution) which was effective in doses ranging from 0.05 cc. to 1 cc., treatment being continued until the sinuses had healed and the adenopathy subsided. Six to 12 doses were usually necessary. The antigen has also been given intravenously by several observers, the most recent report being that of de Gregorio,[35] who treated 50 patients with more rapid results, following 12 to 14 injections, than by any other method.

Convalescent serum was employed by Katz and Sagher[52] with favorable results, but there have been no further reports of this method apparently. Thomas and McCarthy[118] employed a bouillon filtrate of hemolytic streptococcus and other organisms obtained from the wound in 1 case, with healing in 2 months. The uncertain interpretation of such results in view of spontaneous cure is obvious. Chaulmoogra oil was used by Landrock[58] without results. The surgery of the hypertrophic and elephantiasic manifestations and the management of rectal stricture is a special field in which results are largely dependent on skill and experience, for the tissue in most cases heals satisfactorily. It must be borne in mind that all the forms of treatment previously discussed are asserted to exercise some beneficial influence and are asserted to improve the outlook both objectively and symptomatically. Surgery should therefore be a secondary rather than a primary resort in present-day practice.

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PHYSIOLOGY.

PROCEEDINGS OF
THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA
SESSION OF FEBRUARY 20, 1939

The Effect of Progressive Sympathectomy on the Hypertension Produced by Increased Intracranial Pressure. NORMAN E. FREEMAN and WILLIAM A. JEFFERS (Harrison Department of Surgical Research and the Robinette Foundation, University of Pennsylvania). The intracranial pressure was raised, in dogs anesthetized by nembutal, by intracisternal injection of sterile physiologic salt solution at 200 mm. Hg. pressure. The blood pressure was recorded from the femoral artery by means of a Hamilton manometer. In normal dogs, the systolic pressure increased to over 300 mm. Hg. and the diastolic increased from 120 to 180 when the cisternal pressure was raised to 200 mm. Hg. The dogs were then allowed to recover before being subjected to progressive sympathectomy under aseptic precautions in successive operations under ether anesthesia. They were tested again after each stage of the sympathectomy.

Sympathectomy of the splanchnic area by lower thoracic ganglionectomy (T9 to T13) or by upper lumbar ganglionectomy (T13 to L2) and splanchnicectomy did not prevent the development of hypertension. Neither did upper thoracic sympathectomy (T1 to T6) prevent the rise in blood pressure.

When both upper thoracic (T1 to T6) and lower thoracic (T9 to T13) sympathetic ganglia were excised, the hypertension from increased intracranial pressure failed to appear. This observation has been confirmed in 4 dogs. They are being tested each month. No recurrence of hypertension was found up to 107 days.

Hypertension produced by increased intracranial pressure was slight when the heart was denervated and the adrenals removed, even though the splanchnic sympathetic innervation was intact.

Extensive sympathectomy (T5 to L5) was performed on 1 dog. The major portion of the vascular bed was sympathectomized by this procedure, but the cardiac nerves were left intact. Four days after the last operation (left, T5 to T13), hypertension did not occur when the cisternal pressure was increased. Sixteen days after the last stage, the systolic blood pressure went up from 160 to 240 mm. Hg. under the same conditions.

Conclusion. Sympathetic cardiac innervation, neural or humoral, is necessary for full development of hypertension produced by increased intracranial pressure.

The Non-specificity of Suspensions of Sodium Xanthine in Protecting the Liver Against Injury by Chloroform, and the Probable Cause of its Action. I. S. RAVDIN, SAMUEL GOLDSCHMIDT and HARRY M. VARS (Harrison Department of Surgical Research, University of Pennsylva-

nia). In 1936 Forbes and Neale reported that they had extracted a substance from the hog's liver which exerted a marked protective action against the hepatic necrosis produced by the inhalation of carbon tetrachloride and chloroform. The active principle of their extract they subsequently reported to be xanthine. Barrett, MacLean and McHenry, and O. G. Fitzhugh have confirmed Forbes and Neale, but while Barrett and his coworkers believe that xanthine accelerates the processes of regeneration, Fitzhugh believes that it exerts a definite protective action against necrosis.

The experiments which we have conducted have been, as a rule, on rats having a fatty acid concentration of the liver by dry weight of approximately 20%. In such rats the incidence of hepatic degeneration or necrosis following 1 hour of chloroform anesthesia is about 90%. When injections of sodium xanthine, xanthine nitrate or colloidal carbon are administered 18 hours before the chloroform to rats with this concentration of liver lipid, the incidence of degeneration and necrosis following 1 hour of chloroform anesthesia is considerably reduced. When sodium ricinoleate is injected complete protection is provided even to starved rats.

The histologic picture at the site of injection varies from mild to moderate leukocytic infiltration to abscess formation. We are led to conclude that xanthine is not a specific protecting agent, but that any substance which sets into motion processes of protein catabolism in the organism will either prevent necrosis, aid in regeneration, or play a part in both. It is our opinion that the mechanism involved in these experiments is probably similar to that which has been described by Daft, Whipple and Robscheit-Robbins who found that the production of an acute sterile abscess stimulated the formation of hemoglobin in anemic dogs.

The Nature of Certain Changes in Cell Permeability Produced by Alcohols. M. H. Jacobs and A. K. Parpart (Department of Physiology, University of Pennsylvania, and Department of Biology, Princeton University). The present experiments emphasize the need of great caution in attempting to base theories of narcosis on any supposedly general permeability-decreasing or permeability-increasing effect of narcotic substances. Using concentration of n-butyl alcohol of from M/4 to M/128 at 20° C., we have found that whereas the permeability to glycerol of the erythrocytes of the rat, rabbit, guinea-pig, man and several other species is decreased, the opposite effect is obtained with those of the ox, sheep, horse, pig, dog, cat, and so on. Furthermore, even with erythrocytes of the same species the effect produced may be very different with different penetrating substances. Thus, over the range and at the temperature in question, the permeability of human erythrocytes to ethylene glycol, like that to glycerol, is decreased by n-butyl alcohol, though to a lesser extent, while that to diethylene glycol and triethylene glycol are increased; that to monoacetin is slightly decreased over a part of the range and increased over the remainder, and that to diacetin is not much changed. Permeability to none of these substances is decreased in the case of the erythrocytes of the ox. Erythrocytes of all the mammals so far studied are made more permeable

to thiourea by n-butyl alcohol, a substance in which thiourea is somewhat soluble, but are made much less permeable to ammonium salts of the mineral acids. The decreased permeability to the latter substances, previously inferred from observations of hemolysis, has been confirmed by direct studies, by a photoelectric method, of the prehemolytic volume changes of the cells. Presumably the effect is one of decreased permeability of the cell to anions, since such an effect can also be demonstrated by studies of the $Cl\text{-}SO_4$ exchange in solutions of sodium salts, and since it seems to be completely lacking in the case of ammonium salts of weak acids which through hydrolysis are able to penetrate cells in a non-ionic form.

The Character of Growth of Frog Carcinoma in Tissue Culture (With Motion Pictures). BALDUIN LUCKÉ (Laboratory of Pathology, School of Medicine, University of Pennsylvania). Study of tumors by the method to tissue culture has yielded much information concerning the differences between malignant cells and normal adult cells of the same type. Hitherto, such studies have been restricted to tumors of higher vertebrates. In the present paper are given results of culture experiments with a neoplasm of a cold blooded animal, the leopard frog, which is frequently affected with carcinoma of the kidney. This tumor has the appearance of adenocarcinoma, which when large not uncommonly metastasizes. The outstanding characteristic of this carcinoma is the presence of intranuclear inclusion bodies resembling those found in herpes and other diseases known to be due to viruses. The results of transmission experiments support the view that this tumor is in fact caused by filterable virus.

In the present experiments 32 such carcinomas have been cultured by the roller-tube technique of Gye and Lewis as well as by the ordinary hanging drop method. The roller tube method consists essentially in planting fragments of tissue in a thin layer of plasma attached to the inside of a test-tube. This solid medium with the explants is bathed with a nutrient liquid, which is kept circulating by slow rotation of the tube. The majority of cultures were maintained for about 6 weeks; a few were studied for as long as 16 weeks.

Under these conditions, bud-like projections promptly grow from the tumor explant into the solid medium, where they form structures resembling tubules, except for absence of a lumen. The tubules are at first contained within basement membranes, but later, proliferating epithelial cells break through the basement membrane, and spread out as thin fans of polyhedral epithelial cells. These fuse with other outgrowths of similar character until the explant is entirely surrounded by a thin flat layer of epithelium which shows no trace of differentiation into tubules or acini. It is noteworthy that in this process, stroma and macrophages take little part; the newly formed tissue is almost exclusively epithelium, indicating that it is in these cells that the exaggerated growth energy of the carcinoma chiefly resides. In common with culture of mammalian carcinoma, mitotic figures are frequent, the size of the nucleus is great relative to the cytoplasm, the nucleus is granular and the nucleoli large. However, the size of the cells of the frog carcinoma is distinctly larger than those of most mammalian tumors,

making the present material especially suitable for cytologic study. In addition, the frog carcinoma has the remarkable property of growing quite well over a relatively wide range of temperatures. The cultures flourish not only at room temperature (22° C.), but also at any temperature between 17° and 37°, with the optimum close to 30°.

In contrast to the prompt, rapid and long continued growth of this carcinoma, normal adult frog kidney in tissue culture grew only slowly and to a very limited extent. In these normal explants the epithelium especially showed low growth energy, usually being outstripped by connective tissue and macrophages.

In addition to direct observation, two cultures of the tumor were studied by cinematograph. This method not only affords a permanent record, but makes clearer the manner of outgrowth, the character of locomotion of the individual cells, as well as intracellular changes which occur so slowly as otherwise to escape detection.

Transplantation of Frog Carcinoma in the Eye of the Same and of Alien Species, Studied by Direct Microscopic Observation. Balduin Lucké and Hans Schlumberger (Laboratory of Pathology, School of Medicine, University of Pennsylvania). The characteristics of cancer growth have hitherto been studied chiefly by histologic methods, that is in fixed, sectioned, and stained material. The recent development of slit lamp microscopy makes it now possible to observe the habit of growth of tumors while living. Carcinoma of the kidney of the leopard frog, *Rana pipiens*, has proved admirable material for this purpose. Bits of these tumors are implanted in the anterior chamber of the eye, where they soon establish themselves, and where their rate of growth may be measured, and the form of the tumor as well as the arrangement of the constituent cells may be observed through the cornea by means of the slit lamp microscope. Observation of many such transplanted carcinomas has led to the conclusion that the form which the growing tumor assumes depends on its immediate physical environment. Where the tumor grows out in the midst of the aqueous humor, not in contact with cornea or iris, there the habit of growth is characteristically tubular or papillary, the projections being hollow and cystic in some instances, solid masses of cells in others. If, however, the tumor grows in contact with an even surface such as cornea or iris, then the form of growth is entirely different; broad membranes are formed which extend along and cover the cornea or iris; such growths show no sign of tubule formation, or, at most, abortive tubules appear late in the course of growth.

The statement, so often encountered, that the growth of tumors is anarchic, and that tumors obey no laws, is not borne out by these observations. Here is a cancer, which, while growing in the frog's kidney, is typically malignant, invasive, not seldom metastasizing. Yet when transplanted in the eye, its habit of growth is distinctly influenced by its physical environment, by the nature of the space in which it grows, the surfaces with which it is in contact; in other words, this raises the question to what extent neoplastic tissues obey the same physical laws as do normal tissues.

Transplantation of tumors into other species of animals has rarely been successful. However, we have been able to grow these tumors of the leopard frog in the anterior chamber of several species, the green frog (*Rana clamitans*), the bull-frog (*R. catesbeiana*) and the toad (*Bufo americanus*). Transplanted into the eyes of these species, the tumors grew at approximately the same rate and assumed the same forms as in the original species.

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